Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

BOTULINUM TOXIN

Botox, Dysport

UK/W/0100/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	17/04/2018
Finalisation of PAR:	17/05/2018

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section X
INN (or common name) of the active substance(s):	Clostridium botulinum toxin
MAHs:	See section X
Pharmaco-therapeutic group (ATC Code):	M03AX01
Pharmaceutical form(s) and strength(s):	Powder for solution for injection 50U, 100U, 200U Powder for solution for injection 300U, 500U

I. EXECUTIVE SUMMARY

Two marketing authorisation holders (MAHs) submitted paediatric data for botulinum toxin, in accordance with an Article 45 of Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use. The UK is the rapporteur for this procedure. The MAHs are:
MAH1: Ipsen
MAH2: Allergan

Botulinum toxin acts by blocking peripheral cholinergic transmission at the neuromuscular junction and has been widely used for over 20 years in adults and children for a variety of indications including spasticity, focal dystonias, bladder disorders, hyperhidrosis, siallorhea and many others. Licensed botulinum toxin products contain either type A or type B serotype of the toxin. In the EU botulinum toxin type A is indicated in children for focal spasticity associated with dynamic equinus foot deformity in children with cerebral palsy (CP).

The MAHs stated that the submitted paediatric studies and post marketing safety data do not influence the benefit:risk for botulinum toxin and therefore no consequential regulatory action is needed.

Based on the submitted safety postmarketing data, botulinum toxin is being used off label in children below 2 years and in a range of non-approved indications. In addition, a number of fatal cases have been reported. In many of these cases, it cannot be excluded that treatment with botulinum toxin did not contribute to the adverse outcome.

Based on the reviewed paediatric data, the rapporteur concludes that overall the drug's benefit:risk ratio has not changed in the approved paediatric indication.
The SmPC of Botox has information in section 4.1 and 4.2 that could be misinterpreted with regards to the approved paediatric indications. Taking into consideration the risks, including death, identified for the paediatric population from use of botulinum toxin (including during off label), information on paediatric use should be clear throughout the SmPC and according to the 2009 SmPC guideline.

The SmPC of Dysport in section 4.4 does not contain sufficient information regarding potential systemic adverse events in children and the rapporteur has proposed wording to be added in this section.

MAHs for BTX products should continue monitoring ADRs in children, both in the licensed indication and during off label use. Serious cases, including fatal cases, should be submitted in detail via the appropriate PV regulatory procedures to ensure identification of potential new safety concerns and signals and if needed, further regulatory actions should be taken.

SmPC changes are proposed in sections 4.4 (Dysport) and 4.2 (Botox).

Summary of outcome

- ☐ No change
- ☐ New study data

☐ New safety information

☒ Paediatric information clarified: sections 4.2, 4.4

☐ New indication

SmPC changes proposed by the rapporteur (New text is in bold and underlined)

1. Dysport:

Section 4.4:

Paediatric population
For the treatment of spasticity associated with cerebral palsy in children, Dysport should only be used in children of 2 years of age or over. Post-marketing reports of possible distant spread of toxin have been very rarely reported in paediatric patients with comorbidities, predominantly with cerebral palsy. In general the dose used in these cases was in excess of that recommended (see section 4.8).
There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin, including following off label use (e.g. neck area). Extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease. Treatment in patients with poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks.

2. Botox:

Section 4.2:

Paediatric population

The safety and efficacy of BOTOX ~~in the treatment of individual indications have not been established in children and adolescents under the ages listed in the table below. No data are available.~~ **in indications other than those described for the paediatric population in section 4.1 have not been established. No recommendation on posology can be made for indications other than focal spasticity associated with paediatric cerebral palsy. Currently available data per indication are described in section 4.2,4.4, 4.8 and 5.1 as shown in the table below.**

• Focal spasticity associated with paediatric cerebral palsy	2 years **(see section 4.2, 4.4 and 4.8)**
~~• Upper and lower limb spasticity associated with stroke~~	~~18 years~~
• Blepharospasm/Hemifacial spasm	12 years **(see section 4.4, 4.8)**
• Cervical dystonia	12 years **(see section 4.4, 4.8)**

~~• Chronic migraine (CM)~~	~~18 years~~
~~• Overactive Bladder (OAB) and Neurogenic Detrusor Overactivity (NDO)~~	~~18 years~~
• Primary hyperhidrosis of the axillae	12 years (limited experience in adolescents between 12 and 17 years, see sections **4.4,** 4.8 and 5.1)

II. INTRODUCTION

MAH1 submitted completed paediatric studies for botulinum toxin type A haemagglutinin complex (BTX-A-HAC), in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use. A short critical expert overview has also been provided. MAH2 confirmed that the paediatric studies completed prior to January 2007, have been previously submitted to EU competent authorities either during Marketing Authorisation Applications (MAAs) or within Periodic Safety Update Reports (PSURs).

Botulinum toxin type A (referred to as BTX-A in this report) is produced by the bacterium Clostridium botulinum and acts to inhibit the release of acetylcholine at neuromuscular synapses, resulting in chemo-denervation and relaxation of the injected muscles. The effect is temporary and is usually reversed within 3 months due to regrowth of the terminal buds. The therapeutic value of BTX-A derives from its ability to specifically and potently inhibit involuntary muscle activity over an extended duration of time.
MAH1's product is formulated as a complex with haemagglutinin, a large therapeutically inert protein (BTX-A-HAC).

BTX-A-HAC (Dysport) is indicated for symptomatic treatment of focal spasticity of:

- Upper limbs in adults
- Lower limbs in adults affecting the ankle joint due to stroke or traumatic brain injury (TBI)
- Dynamic equinus foot deformity in ambulant paediatric cerebral palsy patients, two years of age or older.

Dysport is indicated in adults for symptomatic treatment of:

- Spasmodic torticollis
- Blepharospasm
- Hemifacial spasm
- Severe primary hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics.

BTX-A (Botox) is licensed for the following indications:

<u>Neurologic disorders:</u>

• treatment of focal spasticity, including:

➢ dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older

➢ wrist and hand disability due to upper limb spasticity associated with stroke in adults

➢ ankle disability due to lower limb spasticity associated with stroke in adults

• symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis)

• prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)

<u>Bladder disorders:</u>

• management of bladder dysfunctions in adult patients who are not adequately managed with anticholinergics

➢ overactive bladder with symptoms of urinary incontinence, urgency and frequency

➢ neurogenic detrusor overactivity with urinary incontinence due to subcervical spinal cord injury (traumatic or non-traumatic), or multiple sclerosis

<u>Skin and skin appendage disorder:</u>

• management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics.

Another BTX-A product is Xeomin which is indicated only in adults for the symptomatic treatment of blepharospasm, cervical dystonia of a predominantly rotational form (spasmodic torticollis) and spasticity of the upper limb. There are also other BTX-A products for cosmetic use only. Botulinum toxin type B (Neurobloc) is also available and indicated for the treatment of cervical dystonia (torticollis) in adults but is not licensed for use in children.

Paediatric investigation plans (PIPs) have been agreed for the following indications:
- Treatment of muscle spasticity in cerebral palsy (in upper and lower limbs) in children over 2 years (EMEA-001039-PIP01-10-M02, active substance: Clostridium Botulinum neurotoxin type A, free of complexing proteins),
- Treatment of chronic sialorrhoea associated with neurologic conditions and/or intellectual disability in children over 2 years (EMEA-001039-PIP02-12-M02, active substance: Clostridium Botulinum neurotoxin type A, free of complexing proteins)

PIP waivers have been issued for products that were intended only for cosmetic indications, i.e. glabellar lines/skin wrinkling/muscle induced wrinkles.

III. SCIENTIFIC DISCUSSION

III.1 Information on the pharmaceutical formulation used in the clinical studies

MAH1: Botulinum toxin type A-haemagglutinin complex (BTX-A-HAC, Dysport) also contains lactose and human albumin and is supplied as a lyophilised powder. BTX-A-HAC powder is available in vials of 300 Units U or 500 U for reconstitution with 0.9% sodium chloride.

MAH2: The formulation (Botox) contains BTX-A, human albumin and sodium chloride.

The Botox SmPC mentions: “Botulinum toxin units are not interchangeable from one product to another”. A similar statement is found in the SmPC of Dysport: “The units of Dysport are specific to the preparation and are not interchangeable with other preparations of botulinum toxin.”

Rapporteur’s Comments:
The same formulation is used in children and adults. MAH1 submitted studies conducted with the Dysport formulation.

III.2 Non-clinical aspects

No animal data have been submitted by the MAHs.

III.3 Clinical aspects

MAH1 submitted the following studies:

A. Postmarketing non-interventional studies with paediatric patients

1. Study A-38-52120-102

Title: Dysport post marketing surveillance study

Study Design:

This study aimed to investigate the safety of Dysport treatment in clinical practice for any approved indication. The study was conducted between September 2001 to July 2005 across 24 investigational sites in the Republic of Korea. Eligible subjects were either adults with blepharospasm, hemifacial spasm, spasmodic torticollis or post stroke arm spasticity; or ambulatory children aged 2 years or older with dynamic equinus foot deformity due to cerebral palsy (CP). Dysport dose was administered as per the indication based on investigator's clinical evaluation and did not exceed a total of 1000 U for paediatric subjects. The treatment duration followed normal clinical practices, and subjects were retreated with Dysport based on the investigator's clinical judgement. Safety assessment included all AEs reported during the study period. Overall safety assessment was categorised as 'safe', 'some safe' and 'suspected'. Effectiveness measures included assessment of improvement in clinical symptoms pre- and post-treatment. Global assessment of effectiveness was categorised as 'notably improved', 'improved', 'not changed', 'little worsened', 'worsened' or 'evaluation impossible'. In addition, the final overall evaluation of treatment taking into account both the safety and effectiveness assessments, was categorised as 'very effective', 'effective', 'some effective' or 'not effective'.

Results: Overall, Dysport, in subjects with blepharospasm, hemifacial spasm, spasmodic torticollis, post-stroke arm spasticity and dynamic foot deformity due to CP was well tolerated and effective. Dysport resulted in an 'improvement' or 'notable improvement' in the clinical symptoms of 98% of subjects. There were no new adverse drug reactions or safety findings.

Summary of Results in Paediatric Subjects:

Of a total of 644 subjects treated with Dysport, 55 (8.5%) subjects were treated for dynamic foot deformity due to CP and of these, 5 (9.1%) received re-treatment with Dysport. Of the 55 subjects, 49 were aged 1-9 years old, 3 were 11-18 years old and the remaining 3 were >18 years old. The median dose injected in subjects treated for dynamic foot deformity was 500 U (range: 200 to 1000 U across both treatments). 3 subjects were retreated before the treatment interval specified in the SmPC, i.e. at 7, 8 and 31 days after the first injection; none of the subjects reported any AEs. For one case different muscle groups had been injected at each injection session (since muscles previously injected did not result in sufficient relief of severe spasticity). Other instances were a reflection of the standard clinical practice at the investigational site, where in severe cases, it was usual to inject Dysport on a weekly basis over the period of hospitalisation (in combination with rehabilitation therapy and close monitoring), and, in the experience of the investigator, this was unlikely to cause any AEs.

An additional 10 subjects, aged 1-18 years, received treatment with Dysport for indications other than CP: 6 subjects aged 1-9 years, of whom 4 were treated for torticollis and 2 for post-stroke arm spasticity with doses between 50 to 500 U, and 4 subjects aged 10-18 years, of whom 3 were treated for post-stroke arm spasticity and one for torticollis with doses between 150 to 1000 U. Of these, except for a year-old subject who experienced mild drooling, none of the other subjects experienced any AEs.

All 55 (100%) subjects treated with Dysport for dynamic foot deformity due to CP reported treatment effectiveness, categorised as 'very effective' in 21 (38.2%) subjects, 'effective' in 30 (54.5%) subjects and 'some effective' in 4 (7.3%) subjects.

Of the 55 subjects treated for dynamic foot deformity due to CP, 5 (9.1%) subjects reported AEs. Brief narratives for these 5 subjects were provided by the MAH. Reported AEs included moderate hypotonia, moderate lethargy, asthenia, eyelid ptosis and moderate finger flexor muscle spasticity.

The events were considered by the investigator as probably or definitely related to treatment. All patients recovered from the events. Most of the reported AEs were consistent with the known safety profile of the drug and its pharmacodynamic action.

In addition, another 1-year old male subject (019-585) who was treated with Dysport for spasmodic torticollis (off-label) reported mild drooling considered by the investigator as possibly related to treatment. The event lasted 3 days and the patient recovered without any treatment. The treatment effectiveness was assessed as 'improved' and the overall evaluation as 'effective'.

Rapporteur's comments:
This was a post marketing study that recruited mainly adult patients and 65 paediatric patients. The main indication for the treatment in children was dynamic foot deformity due to CP which is the licensed indication in children above 2 years of age.
Doses used in children were up to 1000U. This is the maximum licensed dose in children: Dysport SmPC: "The maximum total dose of Dysport administered per treatment session must not exceed 15 units/kg for unilateral lower limb injections or 30 units/kg for bilateral injections. In addition, the total Dysport dose per treatment session must not exceed 1000 units or 30 units/kg, whichever is lower. The total dose administered should be divided between the affected spastic muscles of the lower limb(s)."
The range of doses is not presented as U/kg so it cannot be concluded if patients exceeded the maximum recommended dose.

In section 4.4 the SmPC mentions: "For the treatment of spasticity associated with cerebral palsy in children, Dysport should only be used in children of 2 years of age or over." Children below 2 years of age participated in the study, but their exact number is not provided.

3 children were retreated with Dysport before the treatment interval specified in the SmPC, i.e. at 7, 8 and 31 days after the first injection; Although no AEs were reported in these patients, retreatment at such short intervals is not recommended by SmPC: "injections may be repeated every 12-16 weeks or as required to maintain response, but not more frequently than every 12 weeks." Higher frequency of administration may lead to overdose and exaggerated AEs and may lead to greater incidence of antibody formation.

Overall, the AEs reported in children are consistent with the side effects mentioned in the SmPC. No new safety concerns were identified in this study.

2. Study A-38-52120-114

Title: A post marketing survey for evaluating safety of Dysport in Korea patients suffering from Spasticity or Dystonia

Study Design:

This study was conducted between August 2006 to March 2007 across 13 investigational sites in the Republic of Korea. Eligible subjects were adults or children over 2 years of age scheduled to receive Dysport for a particular indication as per the routine treatment practice and in accordance with the drug's SmPC. Safety was evaluated by AE monitoring; no effectiveness parameters were recorded in this study.

Results: Overall, Dysport was found to be well tolerated. Few treatment emergent adverse events (TEAEs) were reported during the study and were consistent with the known safety profile of Dysport. There was some off-label use recorded in the study, however no new safety information was detected.

Summary of Results in Paediatric Subjects:

Of a total of 481 subjects treated with Dysport in the study, 213 (44.3%) subjects were aged <18 years. In addition, another 2 subjects were aged ≥18 to <19 years. 156 of the paediatric subjects were treated for equinus spasticity due to CP; the remaining were treated for other indications including leg and/or arm spasticity due to CP, post-stroke arm spasticity, post-traumatic brain injury arm spasticity, spasmodic torticollis and indications in combination with equinus spasticity due to CP. A total of 16 (3.3%) subjects aged <2 years received treatment off-label for CP equinus spasticity (N=12; 2.5%), spasmodic torticollis (N=3; 0.6%) and hemifacial spasm (N=1; 0.2%). The median dose for the 156 subjects treated for equinus spasticity due to CP was 500 U (range: 90 to 1200 U); 4 subjects (2.1%) received doses >1000 U and no AEs were reported in these 4 subjects.

Of the 213 paediatric subjects, only one 4-year old female subject treated with 500 U of Dysport reported a treatment related AE of pain in extremity of mild intensity but recovered from the event on the same day.

Rapporteur's comments:
In this post marketing safety study 213 paediatric patients were dosed with Dysport and there were no new safety findings.
It is noted that there was off label use of the product as children younger than 2 years were treated and children were treated for conditions other than equinus spasticity. In addition, in 4 patients, doses above 1000U (up to 1200U) were used which are above the SmPC recommended doses.

3. Study Y-47-52120-093

Title: A post marketing surveillance study of Dysport formulated with a batch of bulk active substance from a new primary manufacturing facility.

Study Design:

The study was conducted between October 2004 to July 2006 across 33 investigational sites (Russia, France, Germany). The selection of Dysport dose, the injection sites and the follow-up period for each subject was decided by the treating physician per the routine treatment practice and in accordance with the Dysport SmPC. Safety was assessed by collection of AE data at 4 weeks post-treatment by a telephone call followed by the next scheduled clinic visit at which the safety and treatment effectiveness were assessed. Effectiveness was categorized as: very good/good/moderate/poor.

Subjects: Adults or children over 2 years of age.

Results: Overall, Dysport was found to be well tolerated and effective in treatment of a variety of indications. All subjects completed the study. No new safety concerns were identified. Effectiveness was assessed as 'good' or 'very good' in the majority of subjects.

Summary of Results in Paediatric Subjects:

Of a total of 783 subjects treated, 45 (6%) subjects were treated for equinus spasticity due to CP. The mean age of subjects with equinus spasticity due to CP was 6.0 years (median: 4 years; range: 2 to 14 years) and the mean dose administered was 192.9 U (median: 200 U; range: 60 to 500 U).

Investigator's overall assessment of effectiveness was 'very good' in 12 (27%) subjects, 'good' in 30 (67%) subjects and 'moderate' in 3 (7%) subjects.

A total of 5/45 CP subjects (11%) reported any TEAE: respiratory syncytial virus infection in 3 subjects (of mild intensity in one and moderate intensity in 2 subjects; all events resolved within 7 days); acute tonsillitis (mild intensity, resolved after 8 days) by one subject; The TEAEs were considered treatment-related by the investigator only for one subject (2%) who reported moderate injection site pain (started on the day of injection and resolved on the same day) and subcutaneous haematoma (started 1 day after Dysport injection, lasted for 7 days). There were no severe TEAEs or SAEs reported and none of the TEAEs led to withdrawal of the subject.

Rapporteur's comments:
45 paediatric patients were treated in this post marketing study. No new safety concerns were identified. Dysport was used in children only within the licensed indication.

4.Study Y-97-52120-022

Title: Clinical experience of botulinum toxin (Dysport) treatment in Germany: a one-year post-marketing surveillance report

Study Design:

This study reviewed all data on effectiveness and safety collected by German physicians over a period of one year from September 1993 to September 1994. Both effectiveness as well as tolerability of treatment with Dysport was assessed by the investigator as 'very good', 'good', 'moderate' or 'poor'.

Subjects:

Data were collected on 1939 subjects who received 3352 treatments with Dysport within the study period. Since different focal and segmental dystonias had been treated, the subject population was categorised based on the sites of injection. Of the 1939 subjects treated, a total of 990 (51%) subjects were treated for spasmodic torticollis, 781 (40%) treated for blepharospasm or hemifacial spasm and 55 (3%) treated for upper limb spasticity; the remaining 116 (6%) subjects were treated in various other injection sites or a combination of sites. Subjects in this survey received a maximum 7 injections (for neck muscles) and a mean of ≤2 injections for various muscle groups injected. The median age of subjects was 55 years (range: 12 to 87 years) and there were more females (58%) than males (42%). The median dose for the periocular muscles was 140 U (including both unilateral and bilateral injections) and 640 U for the neck muscles.

Results:

Overall, Dysport was well tolerated and effective. Dysport effectiveness was assessed as 'very good' or 'good' in 74% of subjects, and the tolerability to Dysport was assessed as 'very good' or 'good' in almost 90% of the subjects. The majority of adverse events were both expected and were well tolerated.

Summary of Results in Paediatric Subjects:

No analysis for the treatment safety or effectiveness by age group was performed in the study; analysis was only performed by muscle groups injected but no category was presented for the lower limb muscles. Of the 1939 subjects treated, only 3 subjects were aged <18 years and all 3 subjects received Dysport injections outside of lower limb. Brief narratives for these 3 subjects are presented below, details for which have been taken from the data listings:

• A 12-year-old male subject who received a single treatment with 150 U of Dysport for hand dystonia in the external carpi radialis and external carpi ulnaris muscles. The subject reported moderate paresis 3 days after treatment and was considered definitely treatment related by the investigator. The event was ongoing at the cut-off period for this survey report. The response to treatment was assessed as 'good'.
• A 16-year-old male subject who received a single treatment with 750 U of Dysport for 'generalised dystonia' into the neck. This subject did not experience any AEs. The response to treatment was assessed as 'very good'.
• A 16-year-old male subject who received a single treatment with 500 U of Dysport for torticollis, into the neck. This subject did not experience any AEs. The response to treatment was assessed as 'very good'.

Rapporteur's Comments:
This was a large, one-year post marketing surveillance study; however very limited paediatric data were collected as only 3 children were treated (aged 12-18 years). In all 3 cases the drug was used off label, the indications being torticollis, hand dystonia and generalised dystonia.
No new safety concerns were identified in this study.

5.Study Y-97-52120-029

Title: Clinical experience of botulinum toxin (Dysport) treatment for spasmodic torticollis in Germany. A one-year post-marketing surveillance report

Study Design:

This study reviewed safety and effectiveness data collected by 51 German centres over a one-year period from October 1995 to October 1996 on the use of Dysport in spasmodic torticollis. Data were collected as number of injections and hence total number of subjects could not be calculated. Both effectiveness as well as tolerability of treatment was assessed by the investigator as 'very good', 'good', 'moderate' or 'poor'.

Subjects:

Data were collected for 2007 Dysport injections within the period of 1 year. The median age of subjects was 53 years (range: 3 to 94 years), and there were more females (57%) than males (43%). The median dose was 600 U (range: 70 to 2000 U).

Results:

Overall, effectiveness for 77% of injections was either 'very good' or 'good' and was classified as 'poor' in 6% of treatments. 15.3% of the treatments were associated with AEs. The most frequently reported AEs were swallowing difficulties (8.57%) followed by neck weakness (4.48%). The majority of the AEs were mild or moderate in intensity with 6% of events categorised as severe. There were no serious AEs reported. The majority of the events resolved within 14 days of treatment.

The tolerability to Dysport treatment as judged by the investigator was rated as 'good' or 'very good' for 96% of injections, and in fewer than 1% of treatments were rated as 'poor'.

Summary of Results in Paediatric Subjects:

Of the 2007 Dysport treatments recorded, 7 treatments were given to subjects aged ≤18 years. No analysis for the treatment safety or effectiveness by age group was performed in the study; None of the subjects, who were aged between 3 to 18 years and received between 380 U to 500 U of Dysport for the treatment of different forms of torticollis (rotational/laterocollis/complex form),

reported any AEs. With the exception of one treatment given to a subject for whom no data on the outcome were recorded, the tolerability was rated as 'very good' and effectiveness as 'good' for all other paediatric subjects.

Rapporteur's Comments:
In this study patients were only treated for torticollis which is not a licensed indication in children. 7 treatments were given to patients aged ≤18 years but it is not clear how many patients were dosed and of these patients, how many were in children (<18 years). Limited paediatric data are provided from this study.
Of note in adults, swallowing difficulties were observed in a significant proportion of patients (8.57%). This is a known AE mentioned in the SmPC as "dysphagia" in section 4.8 and characterised as "very common".

B. Clinical Studies in Paediatric Subjects

1.Study Y-97-52120-727

Title: A phase II, randomised, double-blind, dose-ranging, study in children and young people to determine the optimal dose of botulinum toxin type-A (Dysport) in managing the symptoms of hip muscle spasticity due to cerebral palsy

Study Design:

This was a randomised, double blind, parallel-group, dose-finding study in young subjects with hip muscle spasticity due to CP conducted between April 2007 to March 2008 at one centre in the UK. Subjects aged between 4 to 16 years (inclusive) with bilateral hip pain due to CP and a Paediatric Pain Profile (PPP) score ≥25 received a single treatment with one of the 3 doses of Dysport: 5, 10 or 15 U/kg per hip, up to a maximum total dose of 1000 U into each hip. The study medication was injected under ultrasonographic guidance into the adductor magnus, iliopsoas and medial hamstrings of each hip. Up to 40 young subjects were planned to be enrolled, however the study was stopped when 6 subjects had been recruited due to recommendation from the ethics committee to allow only children with bilateral hip pain to be included that led to difficulties in recruitment. The primary endpoint was the change in score in the PPP at Week 4 from Baseline. A responder was defined as having a 20 point reduction in the PPP score. Safety was assessed by monitoring of AEs, vital signs and change in concomitant medication intake. Adverse events were coded using MedDRA.

Subjects:

A total of 6 subjects were treated with Dysport: 2 male subjects in each of the 5 U/kg/hip and 15 U/kg/hip dose groups and 2 female subjects in the 10 U/kg/hip dose group. All 6 subjects completed the study (at Week 16 or Week 20). The age ranged from 7 to 16 years across the dose groups.

Efficacy Results:

4 of the 6 subjects had a ≥20-point reduction in PPP score from Baseline to Week 4, all in the 10 units/kg/hip and 15 U/kg/hip dose groups. In the 5 U/kg/hip dose group, one subject had a ≥20-point reduction in PPP score from Baseline at Week 12 through Week 20 and the other subject had a reduction in PPP score from Baseline at all timepoints but the reduction was <20 points. Some improvement in sleep quality and pattern was observed in 5/6 subjects (no or reduced night time waking) and no analgesic was required for the duration of the study for any subject. No

differences or trends were identified in hip range of movement between the 3 dose groups. One subject in the 10 U/kg/hip dose group had clinically significant pain at Week 16.

Safety Results:

Dysport was well tolerated at all dose levels. There were no deaths, SAEs or AEs leading to withdrawal or discontinuation of study drug. A total of 4/6 subjects (66.7%) reported 8 TEAEs: haemorrhoids and peripheral oedema in one subject; urinary tract infection in one subject; skin lesion in one subject; diarrhoea, vomiting, arthralgia and nasopharyngitis in one subject. No TEAE preferred term was reported in more than one subject. With the exception of one subject in the Dysport 15 U/kg/hip who reported treatment related arthralgia of severe intensity, all other TEAEs were mild or moderate intensity and were considered unrelated to the study treatment by the investigator.

Conclusion:

Overall, Dysport was well tolerated at all dose levels studied. Improvements in PPP score and sleep were observed for some subjects during the study in all dose groups. The greatest improvements in PPP score at Week 4 were observed in the 10 and 15 U/kg/hip dose groups.

Rapporteur's comments:
This study investigated the effect of BTX-A in patients presenting with pain due to hip spasticity. The Paediatric Pain Profile (PPP) is a 20-item behaviour rating scale designed to assess pain in children with severe neurological disability. Patients included in the study needed to have considerable pain (i.e. PPP score ≥25, scores >14/60 may indicate severe pain).
3 doses were tested, 5, 10 ad 15U/kg, the first 2 doses being lower that the licensed dose for lower limb spasticity in children. The study was terminated after recruitment of only 6 subjects due to the requirement imposed by the Ethics committee to include only subjects with bilateral hip pain.
Although Dysport was well tolerated and some effect was reported in the treated subjects, no conclusions can be drawn from this study due to small sample size.

2.Study A-94-52120-094 Pilot (ABO1 Pilot or 094/Dys/7HE50)

Title: A multicentre, open label phase II study to assess the efficacy and safety of botulinum toxin A (Dysport) in the treatment of adductor muscle spasticity in children with cerebral palsy

Study Design:

This was a phase II, open label, single arm pilot study in children with Dysport for the treatment of adductor muscle spasticity due to CP conducted between June 1998 to May 1999 at 8 centres in Germany. This pilot study was conducted to optimise the subsequent prospective, double blind, randomised, placebo controlled phase II Study A-94-52120-094. Subjects aged ≥18 months to ≤10 years with bilateral spasticity of adductor muscles having a Reimers Migration Index (RMI) <50% received a single injection of 30 U/kg of Dysport into the adductor (2/3 of the total dose) and medial hamstring muscles (1/3 of the total dose), the dose being split between the two legs (with a maximum dose of 500 U per muscle group). Subjects with hemispasticity or having received previous BTX treatment in the adductor and medial hamstrings within the last 9 months or treatment with phenol or surgery on these muscles were excluded. Subjects were followed-up for a period of 3 months. Physiotherapy was allowed during the study, assumed it remained unchanged. The primary endpoint was the passive range of motion ((ROM); abduction and adduction at the hip joint in the extended state) at Week 4 according to the 'Neutral-Null' method. The secondary endpoints included joint status including inter-medial condyli distance (IMCD), goal attainment scale (GAS), Modified Ashworth Scale (MAS), Gross Motor Function Measure, pain

score and parent's questionnaire. Safety was assessed by monitoring of AEs, vitals and concomitant medications. In addition, the absence or presence of the following AEs from a predefined list were recorded at Week 4 and Week 12: dysphagia, feeding with gastric catheter, aspiration pneumonia, modification of the voice, diplopia, reduced head control, generalised muscle weakness, temporary functional deterioration, bladder emptying disorders, and other disorders. The analysis population consisted of any subject who was treated with Dysport.

Subjects:

A total of 16 subjects received a single treatment with Dysport 30 U/kg. Of these, 3 (18.8%) subjects did not complete the study: one withdrew consent (as lost to follow-up after Week 4), one presented with a protocol deviation, and the third subject did not attend the Week 4 visit. The median age of subjects was 5.04 years (range: 1.6 to 8.7 years) and the median weight was 15.5 kg (range: 6 to 25 kg). The majority of subjects were male (13 boys, 3 girls). A total of 11 (68.8%) subjects presented with predominantly lower limb spasticity, while the remaining 5 (31.25%) with spastic tetraparesis. The severity of physical disability was categorised as ≥level III Gross Motor Function Classification Scale (GMFCS) for 11 (73.3%) subjects and CP occurred perinatally in 9 (56.3%) subjects. 6 (37.5%) subjects had moderately or severely impaired cognitive function, 5 (31.3%) subjects could walk without aid, while 8 (57.1%) with aid (2 missing data). The analysis population consisted of 16 subjects.

Efficacy Results:

The mean [95% CI] hip abduction-adduction ROM (with hip and knee extended) increased from Baseline by 8.3° [0.8, 15.8] at Week 4 and by 5.5° [0-3.5, 14.5] at Week 12. For secondary efficacy endpoints, most of the efficacy parameters improved at both Week 4 and Week 12.

Safety Results:

The total dose administered (calculated as 30 U/kg body weight) ranged from 180 to 750 U with a median of 465 U. A total of 8/16 (50.0%) subjects presented with 12 TEAEs. The TEAEs reported were nasopharyngitis reported in 3 subjects, constipation, dysphagia, vomiting, leukaemia in one subject each, influenza and hypersensitivity in one subject, and gait abnormal and asthenia in one subject. Treatment emergent AEs for 2 subjects were considered treatment related by the investigator: severe constipation in one subject (started 2 days after the treatment) and hypersensitivity of moderate intensity (started 118 days after the treatment; this subject also reported mild influenza 5 days after treatment) in the second subject. Leukaemia was the only SAE reported during the study and it was considered not related to the study drug by the investigator. No death was reported during the study. The vital signs remained nearly unchanged at Week 4 and Week 12 compared to Baseline. Amongst the solicited specific AEs, temporary functional deterioration was reported in 3 subjects, generalised muscle weakness in one subject and one subject reported 'other' event.

Conclusion:

This was a pilot study to optimise the subsequent planned, double blind, randomised, placebo-controlled phase II study (ABO1) with identical design. Most the efficacy parameters improved at Week 4 as well as at Week 12. All the TEAEs reported were consistent with known safety profile of Dysport and no unexpected adverse drug reactions were reported.

Rapporteur's comments:

This was a small uncontrolled study investigating the effect of Dysport on hip range of motion. 16 patients were enrolled but 13 completed the study. The total dose in this study was 30U/kg

probably based on results of the previous studies, although justification for the selected dose is not provided.

A review article on “best clinical practice in botulinum toxin treatment for children with CP” (Strobl W et al, 2015) emphasizes the need to have specific aims and goals when treating these children. Tone reduction in a specific muscle group does not define effective treatment unless combined with a clinically relevant result. It is not clear in this study if the treatment goal is preventing hip displacement or improving function or facilitating care of the patient. Measures of activity have been added as secondary endpoints, such as GAS and GMFM.

BTX-A therapy is one of the non-surgical interventions aiming to prevent hip dislocation in children with CP. However, based on available evidence, no recommendation for the use of BTX-A to slow or prevent hip displacement can be made (Miller SD, et al, 2017).

No new safety concerns were identified from this study. Some effect was shown in the primary efficacy outcome (range of motion) but its significance cannot be judged in the absence of a control group.

3.Study A-94-52120-061 (ABO2)

Title: A multicentre, open, prospective study to assess the efficacy and safety of Dysport in the treatment of adductor muscle spasticity in children with cerebral palsy

Study Design:

This was a phase II, open label, single arm study in children with adductor muscle spasticity due to CP conducted between July 1998 to December 2002 at 8 centres in Germany. The duration of the study was 3 months. Subjects aged ≥18 months to≤10 years with bilateral spasticity of adductor muscles having an RMI <50% received a single injection of 30 U/kg of Dysport into the adductor (2/3 of the total dose) and medial hamstring (1/3 of the total dose) muscles, the dose being split between the 2 legs. Subjects with hemispasticity or having received previous BTX treatment in the adductor and medial hamstrings within the last 9 months or treatment with phenol or surgery on these muscles were excluded. Subjects could receive a maximum of 2 injections per muscle with a maximum dose of 500 U per muscle group and were followed-up for a period of 3 months. Stratification was done by age (<6 and >6 years) and mobility (able to walk with or without aids/orthoses and unable to walk). The primary endpoint was the passive ROM; abduction and adduction at the hip joint in the extended state according to the ‘Neutral-Null’ method. The secondary endpoints included joint status (including inter-medial condyli distance, IMCD), goal attainment scale (GAS), pain score and Modified Ashworth Scale (MAS). Safety was assessed by monitoring of AEs from a predefined list that included diplopia, bladder emptying disorders, temporary functional deterioration, generalised muscle weakness, reduced head control, dysphagia, modification of the voice and other (no information was collected on type of events reported under this category). No intensity or start and stop dates for the AEs were recorded in the data listings and no AE coding was performed. The analysis population consisted of subjects who received at least one Dysport injection and had at least one post injection assessment.

Subjects:

A total of 93 subjects were treated at least once with Dysport. The mean age of subjects was 5.35 (±2.61) years and the majority of subjects were male (62.4%). The severity of physical disability was classified as GMFCS level III for 84.7% of the subjects and was CP occurred perinatally for 63.41% of them. At inclusion, the mean (±SD) RMI was 29.41 (±10.32)% for the left hip and 27.66 (±13.35)% for the right hip. The analysis population consisted of 93 subjects.

Efficacy Results:

Subjects treated with Dysport showed an improvement in hip joint status at Month (M) 1 and to a lesser extent at M 3 for the abduction-adduction ROM with hip and knee extended, abduction-adduction ROM with hip and knee flexed, flexion-extension ROM, hip internal rotation, popliteal angle and the IMCD at fast and slow stretch. The functional benefit was also accompanied by a reduction in muscle tone: the proportion of subjects with a MAS≤3 decreased at M 1 and to an even greater extent at M 3 compared with M 0. The majority of the subjects reached at least an intermediate target at M 1 and M 3 according to physicians' assessments of the therapeutic goal.

Safety Results:

A total of 36/93 (38.71%) of subjects reported at least one prelisted AE. The most frequently reported prelisted AE was temporary functional deterioration in 16 (17.20%) subjects followed by modification of the voice in 7 (7.53%) subjects and generalised muscle weakness in 6 (6.45%) subjects; 12 (12.90%) subjects also reported 'other' events. There were no SAEs or deaths during the study.

Conclusion:

The aim of this study was to assess the short-term efficacy and safety of Dysport in treatment of bilateral adductor spasticity due to CP. The results from this study were consistent with the results from the Dysport group of Study Y-94-52120-094. There were significant improvements in the efficacy parameters at M 1 and M 3. Treatment with Dysport was found to be well tolerated and there were no SAEs reported.

Rapporteur's comments:
This study investigated the effect of Dysport on hip joint status in terms of range of movement (ROM). Patients included had bilateral spasticity of adductor muscles.
The degree of hip displacement in CP is generally measured by Reimers' migration percentage. Patients included in this study had a mean RMI around 30% which is a degree of displacement that is still amenable to non-surgical interventions. The majority of patients enrolled had a ≥level III Gross Motor Function Classification Scale (GMFCS). GMFCS is strongly associated with risk of hip displacement. Patients should have been stratified at baseline according to RMI, GMFCS and age. In this study stratification was done based on ambulant status and age.
Subjects treated with Dysport showed an improvement in hip joint status at Month (M) 1 and to a lesser extent at M 3. However, the degree of improvement (i.e. exact change in ROM) is not provided and there is no discussion on the clinical relevance of this change. In the absence of a control group and blinded functional assessments, minimal efficacy conclusions can be drawn from this study.
No new safety concerns were identified.

4. Study A-94-52120-061 Follow-up (ABO2 Follow-up)

Title: Long term follow-up of hip development in the treatment with Dysport of adductor muscle spasticity in children with cerebral palsy: a multicentre, prospective therapy optimization study.

Study Design:

This was an open label, investigator initiated, long-term follow-up study that included subjects from Study A-94-52120-094 Pilot, Study A-94-52120-094 (subjects having received either placebo or Dysport for 3 months for bilateral adductor spasticity) and Study A-94-52120-61, who agreed to

enter an open follow-up period up to 24 months after their inclusion. The 3 studies were very similar in terms of subject population included and Dysport dosing regimen and the same dosing regimen was to be followed in the follow-up study. The study was conducted between July 1998 to December 2002 at 8 centres in Germany. Subjects were to be assessed every 3 months.

The primary efficacy endpoint was the change in RMI from M 0 (i.e. Baseline recorded at entry into each of the original study) which assessed the effect of the treatment on prevention of luxation of the hip joint. The secondary endpoints were the joint status and Modified Ashworth Scale (MAS). Safety was assessed by monitoring of AEs from a predefined list that included diplopia, bladder emptying disorders, temporary functional deterioration, generalised muscle weakness, reduced head control, dysphagia, modification of the voice and other. No intensity or start and stop dates for the AEs were recorded in the data listings and no AE coding was performed. The safety population consisted of those subjects who received at least 2 injections. The efficacy population consisted of those subjects who received at least 2 injections and who had an available RMI value at Baseline (M 0) and after inclusion in the follow-up study (M 12 and/or M 24).

Subjects:

A total of 118 subjects entered the follow-up period: 7 from Study A-94-52120-094 Pilot, 25 from Study A-94-52120-094 and 86 from Study A-94-52120-061. The mean (±SD) age of subjects was 5.42 (±2.41) years and the majority of subjects were male (64.86%). The severity of physical disability was classified as GMFCS level III for 87.39% of the subjects and was CP occurred perinatally for 60.19% of them. At inclusion, the mean (±SD) RMI was 30.22 (±9.96)% for the left hip and 28.65 (±13.66)% for the right hip. The safety population consisted of 118 subjects and the efficacy population consisted of 42 subjects (3 from Study A-94-52120-094 Pilot, 15 from Study A-94-52120-094 and 24 from Study A-94-52120-061).

Efficacy Results:

The long term efficacy could be assessed only for 42 subjects. The mean (±SD) RMI at M 12 compared to M 0 (0.18 (±5.98)%) was mostly unchanged, while it deteriorated slightly at M 24 (2.67 (±12.15)%). There were significant increases in IMCD from M 0 at all visits (M 6, M 12, M 18 and M 24) in both the fast stretch and slow stretch conditions. No significant changes were observed for any other assessments for the joint status at any timepoint. Improvement was noted in the popliteal angle at M 18 (5.57° (±19.50)). The proportion of subjects with a MAS ≥3 in the left and right adductor muscles decreased from M 0 at majority of the timepoints.

Safety Results:

Subjects were followed-up for a mean (±SD) duration of 415.3 (±280.4) days: 38.18% being followed for 0 to 8 months, 20.91% for 8 to 16 months and 40.91% for 16 to 24 months (8 data missing). Subjects received a mean (±SD) of 5.0 (±2.6) Dysport injections: 45.76% received between 2 to 4 injections, 30.51% between 5 to 7 injections and 23.73% between 8 to 9 injections. The mean frequency of Dysport injection administration was every 72.82 (±26.76) days. The total cumulative dose administered per subject during the entire duration of study was: mean=1713.4 (±1310.4) U or 106.07 (±64.64) U/kg and median=1260.0 U (range=300 to 7540 U) or 88.42 U/kg (range=17.9 to 250.1 U/kg). The dose administered per injection per subject during the study was: mean=488.12 (±190.40) U or 28.64 (±3.38) U/kg and median=451.88 U (range=155 to 1200 U) or 30.00 U/kg (range=8.97 to 40.0 U/kg). A total of 56/118 (47.46%) subjects reported at least one prelisted AE. The most frequently reported prelisted AEs were temporary functional deterioration in 23 (19.49%) subjects, modification of the voice in 12 (10.17%) subjects and bladder emptying disorder in 10 (8.47%) subjects; 28 (23.73%) subjects also reported ‘other’ events. The overall AE incidence by number of Dysport injections was higher in subjects receiving 8 to 9 injections (64.24%; N=28) compared with

subjects receiving 5 to 7 injections (50.00%; N=36) and 2 to 4 injections (37.04%; N=54). This trend was also reflected in the analysis of AEs by duration of follow-up: a higher proportion of subjects who were followed for 16 to 24 months reported AEs (57.78%; N=45) compared with subjects followed for 8 to 16 months (47.83%; N=23) and <8 months (38.10%; N=42). There were no SAEs or deaths during the study.

Conclusion:

The aim of this study was to assess the efficacy and safety of Dysport in long term treatment of bilateral adductor spasticity due to CP to support the hypothesis that early institution of treatment has a potential beneficial effect on the development of the joint cavity, thus preventing the lateralisation of the head of the hip. The mean RMI was mostly unchanged at M 12 and slightly deteriorated at M 24. Compared to the natural evolution of the disease over a 24-month period (that is likely to cause deterioration of RMI due to expected growth in the length), no change in RMI actually corresponded to continued and sustained benefit for subjects. No significant changes were found for any other assessment for the joint status at any timepoint except for IMCD in fast and slow stretch condition and for popliteal angle. The overall incidence of AEs was 47.5% for an average follow-up duration of 415 days. The most frequently reported AEs were temporary functional deterioration and modification of voice. The overall incidence of AEs appeared to increase with the number of injections and the duration of follow-up. The number of injections is associated with the duration of follow-up and it is to be expected that the overall incidence of AEs will increase with the duration of follow up as many of the AEs could be related to background comorbidities in the studied population.

Rapporteur's comments:

Hip dislocation is an important and frequent complication in children with cerebral palsy. It leads to significant pain, difficulty sitting and difficulty in positioning and providing care.

The results of studies examining the effect of BTX-A in preventing hip dislocation in CP have been contradictory (Graham HK et al, 2008, Pascual-Pascual SI et al 2003, Pidcock FS et al, 2005, Placzek R et al., 2004, Yang EJ et al. 2008).

In this study the primary efficacy endpoint was the change in RMI, suggesting that the long-term goal was the prevention of hip displacement. The mean RMI was mostly unchanged at M 12 and slightly deteriorated at M 24. However, long term efficacy could only be assessed in less than half of the patients (42/118) and with such a large number of missing data, conclusions about long term efficacy cannot be drawn. In addition, without a control group or at least reliable historical data, neutral effects cannot be named beneficial as the variability of the outcome measure over this period is unknown.

No new safety concerns were identified.

Safety

The MAHs did not provide any additional data on safety, i.e. from post marketing data or from published literature.

Considering potential off label use (children below 2 years of age and/or use in non-licensed indications) of BTX-A products in the paediatric population, following the submission of the initial paediatric data, the MAHs were requested to provide a short overview of all up to date safety paediatric data.

MAH 1:

A search of the MAH's Global Safety Database for post-marketing cases of use of BTX-A-HAC products in paediatric population received up to 31 March 2017 was performed. A total of 307

post-marketing cases of use in paediatric population were retrieved, of which 2 were received from a Health authority, 4 from the literature, 24 from solicited sources and the remaining 277 cases from spontaneous sources.
Of these 307 cases, 145 cases were reported in either an approved paediatric indication or the information on indication was limited but did not suggest off-label use, 14 cases were reported with no known indication and 148 reports were in uses outside of the approved label.
Of the 159 cases reporting labelled or unknown indications, 110 cases were non-serious and 49 cases were serious, including 4 cases with fatal outcome. In the 4 fatal cases, none of the events leading to the patient's death were assessed by the reporter or the MAH as related to the treatment with BTX-A-HAC. Details of the 4 fatal cases are summarised below:

- The first case involved a 4-year-old boy. The patient's medical history included neonatal meningitis, right infantile hemiplegia with facial palsy and ventriculoperitoneal shunt. No concomitant medications were reported. The patient was administered 500 Units of Dysport to the leg muscles for talipes equinovarus. 9 days later the patient developed deglutition disorders, aspiration pneumonia and emesis; he was taken to an emergency unit. Diffusion of the botulinum toxin was considered possible. Subsequently the patient was hospitalised again for vomiting and fever (possible pneumonia) and later for vomiting, and progressively recovered until he deteriorated again. The patient died almost a month after treatment with Dysport.
MAH's comment: The events deglutition disorder and aspiration pneumonia were considered to be indicative of remote effects of toxin. The events of deglutition disorder, pneumonia aspiration and emesis were reported to have resolved. A few days later the patient's condition deteriorated leading to fatal outcome almost one month after treatment with Dysport.

- The second case was received spontaneously from the physician, and later from literature and involved a 6-year-old female patient with infantile cerebral palsy who was administered 600 Units Dysport for leg spasticity. About two days later, she developed generalized weakness, drowsiness, bilateral ptosis, dysphagia and inexpressive face. Around 10 days after the treatment, she was admitted to hospital where she deteriorated. She was diagnosed with atelectasis and nosocomial pneumonia and was intubated with mechanical ventilation due to respiratory insufficiency and was administered intravenous antibiotic treatment. Approximately 1 week later, following improvement of the ventilation function, the patient was extubated, even though there was a residual respiratory insufficiency. At that time, the ptosis had slightly improved and according to her paediatrician, these complications were due to primary hypoventilation caused by Botulinum toxin A. Previously, the patient had received 500 Units Dysport at the same injection sites and she had had the same symptoms and signs, from which she recovered after 2 months. Almost a month later, the patient was reintubated and mechanical ventilation restarted and a new super-infected atelectasis was suspected. Following this, sepsis occurred leading to multi-organ failure. According to the physician, the cerebral palsy with a very significant thoracic deformity, long-lasting hospitalisation and bad general state contributed to recurrent respiratory complications and therefore based on the whole clinical picture, the death was related to the underlying condition and not directly to the toxin but it was a contributing factor. A few weeks later, the patient died consequent to multi organ failure and sepsis.
MAH's comment: The events generalized weakness, drowsiness, bilateral ptosis, dysphagia were considered to be indicative of remote effects of toxin. In addition, it is noted that this patient received a dose of 54.5 U/kg, which is above the maximum 30U/kg recommended in the SmPC.

- The third case was received from physiatrist and concerned a 3-year-old female patient. Her medical history included reflux, epilepsy and mild dysphagia. She had previously received Dysport without anaesthesia. The patient received a single cycle administration of Dysport, associated with co-suspect phenol associated with anaesthesia. One day after injection, the patient died due to pneumonia. The reporting physician did not provide the causality assessment.

MAH's comment: This case contains limited information, however the time to onset (1 day) of death due to pneumonia makes a causal association with Dysport unlikely.

-The fourth case was spontaneously received from a paediatrician and involved a 3-year-old boy with severe cerebral palsy and tetraspasticity who was treated with Dysport for adductor spasticity. He was administered his first injection without any concern. After 3 months, he received a second dose with 30 U/kg bodyweight. 45 days later he was admitted to hospital for high temperature and cough with overproduction of mucus. He had vomiting episode through the PEG probe. An aspiration pneumonia was diagnosed. In further course the patient showed tachycardic episodes and was transferred to the ICU. 12 days later the patient died due to asystole.
MAH's comment: This case contains limited information and based on the available information the events leading to the patient's death were assessed as unrelated to Dysport by both the reporter and the MAH.

Rapporteur's Comments:
MAH1 submitted an overview of post marketing paediatric cases up to 31 March 2017. A total of 307 cases are reported, out of which 159 in labelled or unknown indications. 4 fatal cases were identified. MAH1 stated that none of these 4 cases were assessed as related to the treatment with BTX-A-HAC.
The first case involved a 4-year-old child who developed deglutition disorders, aspiration pneumonia and emesis after injection with Dysport for talipes equinovarus. These effects may be related to treatment as there are known AEs of BTX-A. Although the patient seems to have recovered before further deteriorating, the contribution of the toxin effects in the final fatal outcome cannot be excluded.
Similarly, in the second case which involved a 6-year old girl with CP, generalized weakness, drowsiness, bilateral ptosis and dysphagia were observed after injection with Dysport. The patient later developed nosocomial pneumonia, respiratory insufficiency, sepsis and multiorgan failure and died. The reporter attributed the outcome to the underlying condition of the patient. Although the patient could be in a more fragile state due to the underlying condition, the systemic effects of the toxin and the higher than recommended dose may have resulted a clinical destabilisation of this patient. Based on the narrative provided it cannot be excluded that treatment with BTX-A contributed to the fatal outcome.
For the third case, limited information is provided, however a contribution of BTX-A treatment to the fatal outcome cannot be excluded.
The fourth case involved a 3-year-old boy that died after being admitted with a diagnosis of aspiration pneumonia and developing episodes of tachycardia. Limited information is provided about this case but again a contributory effect of BTX-A in the outcome cannot be excluded given the known AEs of BTX.
Overall, based on the narratives provided, the contribution of BTX-A treatment to the fatal outcome cannot be excluded.

Amongst the 159 cases reporting labelled or unknown indications, the most frequently reported PTs were Asthenia (21 cases), Muscular weakness (19 cases), Eyelid ptosis (16 cases), Pyrexia (13 cases) and Urinary incontinence (13 cases).
A total of 18 out of the 159 cases were considered as remote effects of the toxin. The most frequently reported PTs in these cases were Muscular weakness (6 cases), Asthenia (5 cases), Eyelid ptosis (5 cases), Neuromuscular toxicity (5 cases), Dysphagia (3 cases) and Fatigue (3 cases). 3 of these cases were associated with respiratory disorders and 2 with pneumonia. Of the 18 cases of remote effects of toxin 11 were serious, including two fatal cases. 13 of the 18 cases of remote effect of toxin recovered, the other cases were not recovered at the time of report or the outcome was unknown (4 cases) and the patient died in one case.

Finally, out of those 159 cases, 22 were in patients who received doses above the recommendation of the SmPC. 8 of these cases were considered as remote spread of toxin. The most frequent PTs in these cases were Eyelid ptosis (5 cases), Muscle Weakness (5 cases), Asthenia (4 cases) and Speech disorder (3 cases). In 10 cases the patient had recovered from all the events reported, in 9 cases the patient had not yet recovered from all the associated events at the time of the report or the outcome was unknown, and in 2 cases there were no adverse events reported with the overdose. In addition, one case of the 22 cases of overdose was also associated with remote effects of toxin and led to the patient's death (case described above). There was no other fatal case associated with administration of doses above the recommendation from the SmPC.
The review of these 159 reports did not identify any new safety concern in the authorised population. Asthenia, Muscular Weakness, Influenza-like illness and Urinary incontinence are listed ADRs in this population. The risk of remote spread is also addressed appropriately in the SmPC in both Warnings and precautions and ADR sections.

Rapporteur's Comments:
The 159 cases reported within the labelled indications include known AEs and mentioned in the SmPC. 22 (14%) were in patients who received higher than the SmPC recommended dose.

There were 148 reports in uses outside of the approved label, 99 were non-serious and 49 cases were serious, including 7 fatal cases which are discussed per indication below.
The table below presents the off-label reports per indication and/or type of off label use. Note that some of these cases were in patients who were injected in both labelled and off-label indications, however there are presented only once, in the off-label discussion below.

Indication	Number of cases
Spasticity related:	**44**
- Upper limb spasticity	26
- Lower limb spasticity and/or unspecified:	15
o Children under 2 years	3
o Spasticity not due to cerebral palsy	5
o Non approved muscles injected	7
- Neck	2
- Torso	2
Cervical dystonia	**9**
GastroIntestinal:	**34**
- hypersalivation	21
- palatoclonus	6
- rectal sphincter, intractable constipation, recurrent enterocolitis, gastroparesis, hypertrophic pyloric stenosis, cricopharyngeal muscle and achalasia	1 of each
Hyperhidrosis:	**14**
- axillary	2
- plantar	2
- palmar	1
- palmoplantar	1
- axillary and palmar	1
- unknown	5
Ophthalmology:	**11**
- strabismus	6
- nasolacrimal duct obstruction	3
- Phthiriasis Palpebrarum and corneal ulcer	1 of each
Dystonia	**6**
Muscle spasms:	**5**
- lower limbs	4
- masseter	1
Urology:	**5**

- neurogenic bladder	5
Pain	**2**
Vocal fold motions	**2**
Other off-label uses:	**8**
- Frey's syndrome, displaced mandibular condylar fracture, neurofibromatosis, muscle rigidity, paralytic syndrome, congenital multiplex arthrogryposis, aesthetic and headache	1 of each
Unknown indication with use in unapproved age or muscles:	**7**
- use in children under 2 years	4
- injection in unapproved muscles: pelvic floor (1) and upper limb (2)	3
Total	**148**

The events associated with the most frequent off-label use are described below:

1.Of the 15 cases reporting off-label use in lower limb and unspecified spasticity, 6 were serious with 2 leading to death. Both fatal cases were in patients aged 1 year and in both cases the reporter and the MAH considered the events leading to death as not related to BTX-A-HAC:

- The first case was spontaneously received from a healthcare professional and concerned a 12-month-old female patient with medical history of cerebral palsy and subsequent spasticity of the muscles in the head, neck and the thoracic area on the left side of the body. She had been born prematurely at 26 week's gestation, and had developed periventricular haemorrhage during the immediate postnatal period, provoking convulsive crises and infantile cerebral spastic paralysis. She received Dysport 96 units distributed into 14 injection sites in the trapezius, upper limbs (including the hand) and the lower limbs. 4 days later, a "breath noise" was detected and she was diagnosed with bronchopneumonia. She was started on Mucoflex (ambroxol), Celestamine (betamethasone, chlorpheniramine) and Trimetox (sulfametoxazol, trimethoprim). After 3 days, the patient was admitted to hospital with bronchopneumonia and fever and died due to cardiorespiratory failure on the same day. The physician stated that there was no relationship between the event and Dysport, and the cause of death was reported as infectious bronchiolitis and that the child had presented with a picture of infectious bronchiolitis and that it was this alone that had caused her death.
MAH's comment: The administration of Dysport to children under 2 years in the neck and upper limb is not recommended as the safety profile has not been established. The patient did not present suction or deglutition difficulties between the administration of Dysport and the onset of the bronchopneumonia.

- The second case was received spontaneously from a paediatrician and it concerned a 1-year-old (approximately) female. The patient's medical history included post-natal asphyxial collapse resulting in brain damage and cerebral palsy. The patient's concomitant medications included baclofen, ranidine and paracetamol. At 2.5 months, the patient received a single cycle of Dysport, at a dose of 15 units/kg, which was given for pain associated with spasticity. It was reported that even though Dysport was effective, another treatment cycle was not given as she had too much pain and muscle involvement for the dose of Dysport to be increased. For this reason, the dose of baclofen was increased instead. Approximately 9 months later, the patient died due to respiratory failure. The reporter assessed the death as not related to treatment with Dysport.
MAH's comment: The time to onset between the administration of Dysport and the respiratory failure makes the relationship unlikely. The patient's medical history was a probable contributing factor.

The most frequent PTs reported in cases of off-label use in lower limb and unspecified spasticity were Asthenia (4 cases) and Muscular weakness (3 cases).
A total of 4 out of these 15 cases were considered as remote effects of toxin, none had a fatal outcome. The most frequently reported PTs in these 4 cases were Asthenia, Constipation,

Dysphagia and Muscular weakness (2 cases each). There were no respiratory events associated with the remote effects of toxin. 3 of the 4 cases occurred in patients treated for lower limb spasticity not due to cerebral palsy (including one case where the patient received a dose higher than the SmPC recommendations) and the last case was in a patient injected in muscles not approved in the SmPC. The patient recovered from the events in 2 cases, and the patient had not yet recovered or the outcome was unknown at the time of reporting in the other 2 cases.

2.Of the 26 cases reporting off-label use in upper limb spasticity, 9 were serious with 1 leading to death. The fatal case occurred in a 3-year-old patient and the event leading to death was assessed as not related to BTX-A-HAC:
- The first case was received spontaneously from a physician and concerned a 3-year-old, female patient. The patient's medical history included chronic encephalopathy and cerebral palsy. The patient was administered 450 Units of Dysport for cerebral palsy spastic diparesis with athetoid component in the gastrocnemius and brachial biceps, after a pre-treatment with co-suspect drug Fenol 5% (fenoterol hydrobromide) which was administered to the patient's anterior branch of the left and right obturator nerve, as an anaesthetic. On the same day, after the performed treatment, the patient was released from the hospital with no problems. At home, the patient was a little tearful, so the patient's mother gave her dipyrone, as recommended. 2 days later, the patient didn't wake up, as she passed away. The patient's mother found blood in patient's mouth but denied the presence of vomit or other secretions on the bed. An autopsy was performed. The official cause of death was bronchopneumonia, with generalized visceral congestion detected, together with petechial haemorrhages in serosae.
MAH's comment: The administration of Dysport to children in the upper limb is not recommended as the safety profile has not been established. The time to onset (less than 2 days) between the administration of Dysport and the death due to bronchopneumonia makes the relationship unlikely. The patient's medical history was a probable contributing factor.

The most frequent PTs reported in cases of off label use in upper limb spasticity are Asthenia (4 cases), Dysphagia (4 cases), Muscular weakness (3 cases) and Pyrexia (3 cases). The cases presenting Asthenia, Dysphagia and Muscular weakness were all considered to be remote effects of toxins. The only event PT appearing more than once in the cases not considered to be remote effects of toxin was Pyrexia (2 cases).
A total of 9 out of the 26 cases of off label use in upper limb spasticity were considered as remote effects of toxin and none had a fatal outcome. As mentioned above, the most frequently reported PTs in these 9 cases were Asthenia (4 cases), Dysphagia (4 cases) and Muscular weakness (3 cases). One of these cases of remote effects of toxin was associated with Dyspnoea and another with Respiratory muscle weakness and Aspiration pneumonia. The patient recovered from the events associated with remote effects of toxin in 6 cases, and the patient had not yet recovered or the outcome was unknown at the time of reporting in the other 3 cases.

3.Of the 9 cases reporting off-label use in cervical dystonia, 2 were serious with one leading to the patient's death:
- The first case was received spontaneously from a physician and concerns a female patient, aged approximately 12 years. The patient's concurrent conditions included severe malnutrition and immunodepression. The patient had severe cerebral palsy with dystonia and spasticity not treated for approximately 2 years. The patient presented with severe deformity and contraction in the legs, which prevented good hygiene. The patient was injected with Dysport (450 Units in total) in the neck, the knee flexors and for equinus foot deformity, following unsuccessful physical treatment. There were no complications during the injection procedure. The next day the patient showed great improvement in her head position, with extension of her extremities and was able to sit with help, however the patient presented a flu status with vomiting, fever and cough. The patient was taken to hospital, where 'pneumonic status' was identified. Treatment was started and 48 hours after the Dysport administration the patient died. The cause of death was identified as pneumonia

secondary to broncho-aspiration in a patient with severe malnutrition and immunodepression. Portal hypertension and digestive bleeding were also noted.

The reporter stated the event and death were not related to Dysport as due to the following reasons. The nature of the disease, the nutrition is very poor, and so malnutrition produces immunodepression. The immunodepression makes the patient more susceptible to any infectious process. This injection coincided with a sub-clinical infectious picture, which worsened with time. The reporter added that the administration of botulinum toxin coincided in a young girl with a sub-clinical infectious process and given the situation at the time, even without the injection probably the infection would have generalized and perhaps the outcome would have been the same.
MAH's comment: The administration of Dysport to children in the neck and non-approved muscles in the lower limbs is not recommended as the safety profile has not been established. The time to onset (less than 2 days) between the administration of Dysport and the death due to bronchopneumonia makes the relationship unlikely. The patient's medical history was a probable contributing factor.
The most frequent PTs reported in cases of off-label use in cervical dystonia are Pharyngeal oedema and Dysphagia in 2 cases each, all other PTs were reported only once each. None of the 9 cases were considered as remote effects of toxin.

4.Of the 21 cases reporting off-label use in use in hypersalivation, 11 were serious with 2 leading to death. In both cases the patients experienced pneumonia (1 also had cardiorespiratory failure) and died of the events. The events were assessed as related to BTX-A-HAC:
- The two cases were part of a cluster of 6 cases reporting SAEs following the use of Dysport for an unapproved indication, i.e. sialorrhoea, from a single rehabilitation site in Mexico. In these two cases, both patients (aged 10 and 15 years) were treated with Dysport for the indication LLT of sialorrhoea (PT of salivary hypersecretion). The 10-year-old male patient experienced a serious event of respiratory distress and died of cardiopulmonary failure and pneumonia. The 15-year-old female patient also experienced a serious event of respiratory distress and died of atypical pneumonia. Both the reporter and MAH assessed these events as having a reasonable possibility of being related to Dysport. In the remaining 4 patients, dysphagia was the main event reported; the outcome of the dysphagia events was reported as resolving. 5 of the 6 patients received a total of 150 U divided between the two submandibular glands and the dose for the sixth patient was 100 U. No injection guiding techniques were used for the injection procedure. Based on follow up information received, a total of 17 patients were injected for sialorrhoea at this site on the same day, 6 of whom developed SAEs. All patients were followed up closely by the injecting clinic. No further AEs were reported to the MAH. No quality issues were identified with the injected batch number.
MAH's comment: Sialorrhoea is not an approved indication for Dysport, either for adults or children in any country of the world.
The most frequent PTs reported in cases of off-label use in hypersalivation are Dysphagia (13 cases), and Respiratory distress (3 cases).
In addition, 1 of these 21 cases was considered as remote effect of toxin, without a fatal outcome. The patient experienced Dysphagia, Dry mouth, Muscular weakness and Gait disturbance but no respiratory disorder associated with the remote effects of toxin. She had not yet recovered from the events at time of reporting.

5. Of the 14 cases reporting off-label use in hyperhidrosis, 3 were serious with none leading to death and no case was considered as remote effect of toxins. The most frequent PTs reported in cases of off-label use in hyperhidrosis are Drug effect decreased (5 cases) and Drug ineffective in 3 cases.

6. Of the 6 cases reporting off-label use in palatoclonus, 1 was serious and not leading to death and no case was considered as remote effect of toxins. The most frequent PTs reported in cases

of off-label use in palatoclonus are Therapeutic response unexpected (2 cases) and Speech disorder in 2 cases.

7. Of the 6 cases reporting off-label use in strabismus, none were serious or considered as remote effect of toxin. The most frequent PTs reported in cases of off -label use in strabismus are Eyelid ptosis (in all 6 cases), Strabismus (2 cases) and Drug ineffective in unapproved indication in 2 cases.

The review of 51 cases in the remaining 25 indications and 2 uses outside the label per PLL recommendations unapproved uses in unknown indications did not identify any new safety information. Of these 51 cases, 16 were serious, of which 1 case was fatal and assessed as remote spread of toxin and possibly related to treatment with BTX-A-HAC:
- This case was identified from the literature and concerned a 4-year-old female patient. The patient's medical history, concomitant medication and previous botulinum toxin experience were not reported. The patient received 120 Units of Dysport for paralysis syndrome and 3 days later, the patient had dyspnoea which resulted in death. It was not reported whether the autopsy was performed. The author considered the event as related to Dysport treatment and stated that the mechanism of the event could be related to a systemic spread of toxin, while another explanation could include the association of other drugs used for sedation (sedative used for this patient were unknown).

MAH's comment: The administration of Dysport to children for paralytic syndrome is not recommended as the safety profile has not been established. Limited information available for this case does not allow any further assessment.

A total of 5 out of the 51 cases were assessed as remote effect of toxin in patients treated for different indications: dystonia of the lower limbs, neurofibromatosis, paralytic syndrome (fatal cases described above), spastic bladder and injection in the pectoral area for spasticity. The most frequent PTs reported were Asthenia, Dysphagia, Dyspnoea and Eyelid ptosis (2 cases each). None of the patients experienced both Dyspnoea and Dysphagia. The patient recovered from the events associated with remote effects of toxin in 2 cases, the patient had not yet recovered from all the events or the outcome was unknown at the time of reporting in 2 cases and the patient died in the last case.

Rapporteur's comments:
Out of the 307 paediatric cases identified in the global safety database to March 2017, almost half (N=148) concerned off label use. 49 cases were serious, including 7 fatal cases. It is not clear when the start date of this database is.
One case involved a child who at the age of 72 days was injected with BTX-A. This patient died at the age of 1 year which makes the association of the outcome with the BTX-A treatment unlikely.
For 2 cases limited information is provided (children 10 and 15 years old treated for sialorrhoea), however both patients developed pneumonia and the reporter and MAH assessed these events as having a reasonable possibility of being related to Dysport.
Another case is provided with limited information: a 4-year-old female child treated with Dysport for "paralysis syndrome", developed dyspnoea 3 days later and subsequently died. This case was identified in the literature and the author considered the event as related to Dysport treatment and potential systemic spread of the toxin or to side effects of the administered sedation.
For the other 3 fatal cases, more clinical information is provided. All 3 patients had CP and following treatment with Dysport, as in the previous fatal cases, developed respiratory symptoms and eventually died. In these 3 cases, the reporters did not consider treatment with Dysport related to the fatal outcome as time from treatment until death was only 2 days (in 2

cases) and in the third the patient did not develop deglutition difficulties. The MAH has not explained why death within 2 days could not be a result of distant spread of the toxin. Based on the FDA review of fatal paediatric cases, the following is mentioned in the label boxed warning: "WARNING: DISTANT SPREAD OF TOXIN EFFECT …..The effects of DYSPORT® and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. …."
Based on the narrative of these 3 cases, the rapporteur considers that the contributory effect of Dysport treatment to the fatal outcome cannot be excluded.
Overall, a common denominator of those 6 fatal cases is that all children, after a short period (range 2-8 days) from the treatment with Dysport, developed respiratory symptoms and eventually died.
The remaining serious AEs reported are known effects of BTX-A and are mentioned in the SmPC.

MAH1's Conclusions

A total of 307 cases of use in paediatric population were retrieved, of which 159 cases were labelled or unknown indications and 148 reports were in uses outside of the approved label (e.g. indication, population). The most frequently reported events in the labelled and unknown indication were Asthenia, Muscular weakness, Eyelid ptosis, Pyrexia and Urinary incontinence. Asthenia, Muscular Weakness, Influenza-like illness and Urinary incontinence are listed ADRs in this population.
The most frequently reported events in off-label uses were Asthenia, Dysphagia, Eyelid ptosis and Muscular weakness. All these were coherent with the known safety profile of Dysport and the off-label uses.
Overall there were 37 cases of remote effects of toxin identified in the paediatric population, 27 of them were associated with uses outside of the label (off-label use and/or doses administered higher than recommended, including in the authorised population), and the remaining 10 cases were in the authorised population with no report of doses outside the recommended range being administered. 3 cases out of the 37 had a fatal outcome: one in a patient who received a dose higher than the SmPC recommendations and had underlying conditions that may have contributed to the fatal outcome, another case in a patient treated in an unapproved indication, and the last one where the patient recovered of the remote effects of toxin prior to dying of another event. The risk of remote effects of toxin effects as well as risk minimisation measures are described in the Dysport SmPC in the Warning and precautions and ADRs sections. Remote spread of effects of the toxin is an important identified risk for BTX-A-HAC in Dysport EU RMP. The risk may be reduced by using the lowest effective dose possible and by not exceeding the maximum recommended dose. The product should only be used with caution and under close medical supervision in patients with clinical or subclinical evidence of marked defective neuromuscular transmission (e.g. myasthenia gravis). The product should be administered with caution to patients with pre-existing swallowing or breathing problems.
There was a total of 11 fatal cases (including 3 cases of remote effects of toxin), 2 of the 11 cases were in patient under 2 year-old (both considered not related to the treatment with Dysport), 3 of the 11 cases were in patients treated for lower limb spasticity including 1 in patient treated with a dose higher than the recommendation from the SmPC, and the remaining 6 cases were in unknown or off-label indications.
Overall, the safety profile is as expected in the authorised population. No new safety concern was identified in use in off-label indications. The MAH is currently conducting a Phase III clinical trial in paediatric upper limb spasticity (EudraCT # 2010-021817-22), which is the most reported indication in unapproved use.

MAH2

MAH2 provided currently available information regarding off-label use (children below 2 years of age and/or use in non-licensed indications) in the paediatric population for Botox/Vistabel, described within the latest approved EU Botox/Vistabel PSUR/PBRER (report no. 24), and additionally within the latest approved Botox/Vistabel RMP (version 7.6). The relevant sections from these documents have been submitted and a summary is provided below.

EU Botox/Vistabel PSUR/PBRER (report no. 24)

15.3.8 Pediatric Patients – Off-Label Usage and Higher than Recommended Maximum Dosage

The MAH was asked to continue to review all cases involving off-label usage and higher than recommended maximum dose in paediatric patients for this current reporting period.

Analysis from 01-January-2013 to 31-October-2013

The MAH's Global Safety Database was searched for cases received from 01-January-2013 to 31-October-2013 which included reports of AEs involving paediatric patients administered either Botox or Botox cosmetic.

The search identified 36 case reports involving paediatric patients. 7 of these cases met serious criteria (2 fatal and 5 non-fatal). All 7 cases involving serious events were reported in children who had received Botox for either an off-label indication or at a higher than recommended maximum dose (ranging from 11-20 U/kg) for paediatric patients. All the serious cases included confounding factors or insufficient information to make a causality assessment.

Analysis from 01-November-2013 to 31-October-2015

A search of the MAH's Global Safety Database for reports of AEs involving paediatric patients was conducted for the period 01-November-2013 to 31-October-2015. The search identified 28 spontaneous cases involving paediatric patients and 4 cases received from regulatory agencies. Of these, 23 were classified as serious: one was fatal and 22 were non-fatal. In addition, the recently completed MAH sponsored market survey study identified 102 cases with limited information regarding dosing and other clinical details. There were also 57 literature cases received with multiple cases reported from each publication, with majority of cases (n=33) for the treatment of hypertonic bladder.

Overall, in terms of the number of SAEs cases reported in 30 children, all were reported in children who had received Botox for either an off-label indication or at a higher than recommended maximum dose for paediatric patients. All the cases included confounding factors or insufficient information to make a reasonable causal assessment.

The MAH acknowledges that paediatric patients are a vulnerable population who are at risk for SAEs. This is particularly true of patients with complicated medical conditions.

As some of the reported cases involved injections around vulnerable anatomical structures, it should be noted that, in the Warning and Precautions section of the CCDS 17.0, it is stated that the relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering Botox and care should be taken when injecting in or near vulnerable anatomic structures.

Based on this review, no additional changes will be made to the CCDS. The MAH will continue to monitor both off-label usage and higher than recommended maximum dose in paediatric patients.

Botox/Vistabel Risk Management Plan (version 7.6); extracted from pages 111 to 116:

SVI.6 Specific pediatric issues

SVI.6.2 Potential for off-label pediatric use

SVI.6.2.1 Off-label use in pediatric patients with cerebral palsy and torticollis

Results from the EU and US Drug Utilization Studies (DUS) indicate that overall, extent of off-label use in paediatric patients with cerebral palsy and torticollis is limited. In the 2008 EU DUS, the

most frequently treated indication in paediatric patients was spasticity from cerebral palsy (77%), though in approximately 4% of patients, treatment was in spasticity from stroke, traumatic brain injury and spinal cord injury. Of the 264 paediatric patients in the EU DUS, only 1.5% of paediatric patients were treated for cervical dystonia.

A cumulative review (01 January 1990 to 30 June 2011) of the use of Botox in the treatment of paediatric torticollis, incorporating data from drug utilization studies, the literature, and the MAH's safety database, was completed and presented in PSUR #20. As discussed in the complete analysis and concurred by the assessor, the aetiology of torticollis generally differs between adults and the paediatric population. Approximately 10-20% of all observed dystonias are secondary to another disorder, often cerebral palsy or tardive dyskinesia (Dressler, 2011). Results of the cumulative analysis presented in PSUR #20 revealed that most serious adverse events were reported in patients with a severe underlying neurological disorder, with respiratory-related AEs and seizures being the most commonly reported.

Additionally, a review of all adverse event cases that were reported in any paediatric patient was conducted and presented in detail during PSUR #21 (01 January 2012 to 31 December 2012). Of the 75 paediatric case reports identified, 17 cases met serious criteria, of which two were fatal cases. Both fatal cases were confounded by either the patient's concurrent medical condition (recent severe influenza, history of tuberculous meningitis) and/or recent surgical procedure (bilateral adductor lengthening surgery).

When Botox is injected into the cervical muscles, dysphagia is an expected adverse event due to local pharmacological effects and exaggerated muscle weakness and dysphagia may have more serious consequences in this vulnerable population. The Warnings and Precautions of the CCDS additionally states that adverse effects distant from the site of injection may be observed and may include muscular weakness, ptosis, diplopia, blurred vision, facial weakness, swallowing and speech disorders, constipation, aspiration pneumonia, difficulty breathing and respiratory depression. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in patients who have underlying conditions and co-morbidities that would predispose them to these symptoms.

The MAH acknowledges that paediatric patients with cerebral palsy, including those with torticollis, are a vulnerable patient population at risk for such adverse events. The RMP currently addresses the following risks relevant to paediatric patients with cerebral palsy being treated for torticollis: dysphagia in cervical dystonia and distant spread of toxin.

The labelling also addresses risks relevant to paediatric patients with cerebral palsy being treated for torticollis. The CCDS states that there have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin. Caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease.

Risk minimization measures are further proposed in the Core Safety Profile (CSP). A separate 'Paediatric Use' sub-section has been added to section 4.4 to consolidate warnings relevant to paediatric use. This section consolidates warnings relevant to paediatric use of the product. The MAH also strengthened the wording in the CSP to clarify that a number of routes of administration are unauthorised. Additionally, the warning regarding off-label use in paediatric patients with cerebral palsy treated for torticollis has been moved to the paediatric use section of the CSP as this prevents duplication and clarifies that the use of Botox in paediatric torticollis is off-label.

As noted in the cumulative analysis presented in PSUR #20, the majority of paediatric adverse events reported for the indication of torticollis were received from Japan (52 out of 72 cases). A total of 19 cases reported a fatal outcome, of which all but one was reported from Japan. The majority of these fatal cases (15/19) were received from a non-interventional active post-marketing surveillance program conducted in Japan (a mandatory regulatory authority requirement in Japan for all products). Safety information received from this post-marketing surveillance program was collected regardless if an indication was approved and/or used for off-label purposes. Seriousness and causality were also assessed. Of note, the majority of serious and fatal cases were assessed

as unrelated to the use of Botox by the reporting physician, suggesting that the patient's underlying disease or other factors were the cause of the adverse event.
GSK-Japan, the business partner responsible for Botox pharmacovigilance activities in Japan, confirmed that the treatment of paediatric torticollis (or cervical dystonia in paediatric patients), is not an approved indication in Japan. In the Japanese package insert (JPI), the only paediatric indication approved for Botox is for the treatment of equinus foot due to lower limb spasticity in juvenile cerebral palsy (JCP) patients aged 2 years or older.
The MAH considers that the risk minimization measures proposed in the CSP are adequate in addressing off-label use in paediatric patients with torticollis. The majority of serious and fatal cases were received from a post-marketing surveillance program conducted only in Japan to actively collect any adverse event experienced, regardless of causality or indication. The reporting physicians assessed the majority of these serious and fatal cases as unrelated to the use of Botox, clarifying that the patient's underlying disease or other factors were the cause of the adverse event.
In compliance with FDA's Pediatric Research Equity Act (PREA) requirements, the MAH is evaluating the safety and efficacy of Botox in paediatric patients with upper limb spasticity (Studies 191622-101, 191622-105) and in paediatric patients with lower limb spasticity (Studies 191622-111, 191622-112) secondary to cerebral palsy. These studies will provide additional important safety information for the treatment of limb spasticity secondary to cerebral palsy in patients aged 2 to 17 years.

SVI.6.2.2 Off-label pediatric use in bladder disorders with urinary incontinence
With regard to potential for off-label use of Botox in urological disorders, approximately 5% of paediatric patients were treated in the 2008 EU DUS for urologic indications. The median dose used for neurogenic OAB was 300 U (n=7) and 80 U (n=4) for idiopathic OAB. In the US DUS, there were no paediatric patients being treated for any urological disorders.
Safety and efficacy following use of Botox in paediatric patients with neurogenic detrusor overactivity and in paediatric patients with overactive bladder has not been systematically evaluated by the MAH to date. In compliance with FDA's PREA requirements, the MAH will be evaluating the safety and efficacy of Botox in paediatric patients with urinary incontinence associated with neurogenic detrusor overactivity who are not adequately managed by anticholinergic therapy (Studies 191622-120, 191622-121) and in paediatric patients with urinary incontinence associated with overactive bladder who are not adequately managed by anticholinergic therapy (Study 191622-137). These studies will provide additional important safety information for the treatment of urinary incontinence due to NDO in patients 8 to 17 years and in patients 12-17 years with OAB who have not been adequately managed with anticholinergic therapy.
In addition, as part of an FDA commitment, the MAH will submit semi-annual safety analyses to the FDA (starting in 2013) based on all post-marketing serious adverse event reports in paediatric patients <18 years of age treated with intradetrusor injection of Botox for the indication of overactive bladder (non-neurogenic). These reports will be submitted to the FDA for a period of at least 3 years.

SVI.6.2.3 Off-label pediatric use in chronic migraine
With regard to potential for off-label use of Botox in paediatric chronic migraine, results of the 2008 EU DUS indicate that there were no paediatric patients treated for chronic migraine or any other headache. In the 2010 US DUS, 2 adolescent patients were treated for headache or chronic migraine. In the 2012 US DUS, there were no paediatric patients being treated for headache or chronic migraine.
The MAH sponsored a study to specifically assess chronic migraine prevalence in adolescents (12-17 years of age). Study result indicated that the estimated overall prevalence rate for chronic migraine in adolescents was 0.79% (Grosberg et al, 2007). By applying this rate (0.79%) to age-specific 2008 US and EU population estimates, it is projected that there are *at most* 198,000 US

adolescents and 265,000 EU adolescents suffering from headaches categorized as chronic migraine according to diagnostic criteria established for adults.
In compliance with FDA's PREA requirements, two studies for chronic migraine in adolescents (Studies 191622-103, 191622-108) will provide additional important safety information on the use of Botox in the paediatric population.

Rapporteur's comments:
Based on PSUR data from 01-January-2013 to 31 October 2015, the MAH identified 37 serious cases, which were reported in children who had received Botox for either an off-label indication or at higher than the recommended paediatric maximum dose. Among those, 3 cases were fatal. No narratives are provided for these cases but the MAH stated that all serious cases included confounding factors or insufficient information to make a reasonable causal assessment.
A previous PSUR is also mentioned (No21) covering the period from 01 January 2012 to 31 December 2012, during which 17 serious cases were identified, of which two were fatal. The MAH stated that both fatal cases were confounded by either the patient's concurrent medical condition and/or recent surgical procedure. No PSUR paediatric data are provided for the period before 2012.
In addition to the latest PSUR, the MAH provided relevant paediatric safety information from the latest RMP which reviewed the potential off label use in children in different indications. Of note, treatment of upper or lower limb spasticity is not a licensed indication in paediatric patients for Botox in the US. Paediatric licensed indications in the FDA label are only: "Treatment of blepharospasm associated with dystonia in patients ≥12 years of age" and "Treatment of strabismus in patients ≥12 years of age". The MAH stated that off label use in children is overall limited, however the exact percentage of off label use per indication separately for EU and US (based on the drug utilisation studies) is not provided. Only paediatric off label use in torticollis and urinary disorders is mentioned, which were reported to be 1.5% and 5% respectively in the 2008 EU drug utilisation study. The MAH does not discuss whether AEs and SAEs are reported proportionally more frequent when Botox is used off label compared to when it is used within its licensed indication.
The MAH, following commitments to FDA, plans to conduct paediatric studies in the following indications: upper limb spasticity, lower limb spasticity, urinary incontinence and chronic migraine.

A cumulative review (01 January 1990-30 June 2011) of adverse events in the indication of torticollis (presented in PSUR No20) was completed by the MAH. The majority of paediatric adverse events reported for the indication of torticollis were received from Japan (52 out of 72 cases). A total of 19 cases reported a fatal outcome, of which all but one was reported from Japan. 15/19 cases were received from a non-interventional active post-marketing surveillance program conducted in Japan (a mandatory regulatory authority requirement in Japan for all products). No other details for this surveillance program are provided, i.e. the period it covered and the number of children being treated during that period. Nevertheless, 19 fatal cases is a large number despite the MAH's statement that the majority of the serious and fatal cases were unrelated to Botox treatment. As no case details are presented here, potential association between the fatal outcome and Botox treatment cannot be excluded.

The MAH states that the Botox SmPC clearly states that use of Botox for cervical dystonia is off label in children. In section 4.4 under the subheading Paediatric use", it is stated:
"The safety and efficacy of Botox in indications other than those described for the paediatric population in section 4.1 has not been established. Post-marketing reports of possible distant spread of toxin have been very rarely reported in paediatric patients with comorbidities,

predominantly with cerebral palsy. In general the dose used in these cases was in excess of that recommended (see section 4.8).
There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin, including following off-label use (e.g. neck area). Extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease. Treatment in patients with poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks."
However, in section 4.2 the following is mentioned under the subheading "Paediatric population":
"The safety and efficacy of Botox in the treatment of individual indications have not been established in children and adolescents under the ages listed in the table below. No data are available."

• Blepharospasm/Hemifacial spasm	*12 years*
• Cervical dystonia	*12 years*
• Focal spasticity associated with paediatric cerebral palsy	*2 years*
Upper and lower limb spasticity associated with stroke	*18 years*
• Chronic migraine (CM) 18 years	*18 years*
• Overactive Bladder (OAB) and Neurogenic Detrusor Overactivity (NDO)	*18 years*
• Primary hyperhidrosis of the axillae	*12 years* *(limited experience in adolescents between 12 and 17 years)*

The rapporteur considers that the SmPC information in section 4.2 could be confusing as it might be interpreted that above the ages mentioned in the table, efficacy and safety in children has been established. According to section 4.1, Botox is not licensed in children above 12 years for hemifacial spasm, cervical dystonia and primary hyperhidrosis of the axillae. Section 4.1 and 4.2 of the SmPC should clearly state which indications are licensed in children as different conclusions might be drawn from the current text in the two sections. The MAH should review the SmPC wording in sections 4.1 and 4.2 and propose updates to fully clarify the paediatric indications in line with the SmPC guideline.

Fatal cases with the use of BTX-A continue to be reported. Especially concerning is the number of fatal cases reported from the Japanese active surveillance study, although details of this study are not provided to contextualise these events. The MAHs are asked to confirm that detailed data of all reported fatal cases have been submitted and assessed by regulatory authorities via the appropriate PV procedures (PSUR, RMP).
In addition, both MAHs are asked to continue monitoring adverse events and off label use in children and collect adequate case details to allow assessment of potential causality between BTX-A treatment and AEs and any association with specific indications, dosage and dosage intervals used, different age groups and underlying condition.

3. Discussion on clinical aspects

Botulinum toxin acts at the neuromuscular junction to inhibit the release of the neurotransmitter acetylcholine. Serotypes A and B are available for clinical purpose. BTX-A is licensed in children

for the treatment of dynamic equinus foot deformity in ambulant paediatric CP patients 2 years of age and older, although this indication varies from country to country and among different products. Off label uses of BTX-A in children include other lower limb spasticity, upper limb spasticity, cervical dystonia/torticollis, urinary incontinence, siallorhea, hyperhidrosis and others.
In the UK, only Botox and Dysport are licensed for use in children.

Guidelines

- *European Consensus 2009 on the use of BTX for children with cerebral palsy (Heinen F et al, 2010)*: The consensus mentions that therapy goals should be established prior to therapy. It is also mentioned that "Licensing does not reflect the clinical need, especially for children with CP. Individualised variations in BTX dosage, dilution, clinical indication(s) and the muscle group(s) treated represent appropriate, although unlicensed, use where such treatment is in line with clinical experience. A multi-muscle, multi -level treatment approach is proposed."

- *NICE guideline on "Spasticity in under 19s: management" (2012):* The guideline discusses when BTX-A treatment should be considered in children with focal spasticity of the upper limb and focal spasticity of the lower limb. The Guideline Development Group emphasised the importance of establishing individualised goals that justify the use of this potentially harmful toxin to treat spasticity. It is also mentioned: "When considering botulinum toxin type A treatment, perform a careful assessment of muscle tone, range of movement and motor function to: inform the decision as to whether the treatment is appropriate and to provide a baseline against which the response to treatment can be measured."
"Before starting treatment with botulinum toxin type A, tell children and young people and their parents or carers:
- to be aware of the following rare but serious complications of botulinum toxin type A treatment →swallowing difficulties, breathing difficulties,
- how to recognise signs suggesting these complications are present,
- that these complications may occur at any time during the first week after the treatment and
- that if these complications occur the child or young person should return to hospital immediately."

Regulatory background

In 2006 the EMEA Pharmacovigilance Working Party reviewed cases of distant spread/systemic effects including muscle weakness, dysphagia, and aspiration, observed with the use of BTX-A and BTX-B products. It was then decided that amendments to the SmPCs were necessary to list those distant reactions and include precautions for patients treated. It was also agreed to include in the RMPs of these products detailed strategies for educating physicians and programmes for continued and improved monitoring of spread reactions in clinical use and in clinical trials. The obligation for educational materials for healthcare professionals and patients was agreed by PRAC to be removed in 2016, as it was considered that sufficient experience was gained over the past years and the risks of toxin spread and dysphagia are adequately minimised by the information included in the product information.
In 2009 the FDA completed a safety review of BTX-A and BTX-B products following reports of systemic adverse reactions including respiratory compromise and death when used for both FDA-approved and unapproved uses. The most serious cases occurred mostly in children treated for cerebral palsy-associated limb spasticity.
FDA concluded that the prescribing information should be revised to include a *Boxed Warning* and a *Medication Guide* (for patients/family members and caregivers) that highlight the risk, shared by all of the botulinum toxin products, of spread of toxin effect from the area of injection, causing symptoms similar to those of botulism.
In addition, FDA has agreed to the revised established names for each botulinum toxin product to reinforce the understanding that each product has an individual potency and is not interchangeable with any other product. In the FDA label Dysport is also mentioned in parenthesis as (abobotulinumtoxinA) and Botox as (onabotulinumtoxinA).

In March 2013, a drug safety update article informed on the serious known risks with the use of BTX-B (Neurobloc) and particularly with off label use such as in patients with underlying neuromuscular deficits and in children. The advice for healthcare professionals was to adhere to the licensed indication and not use BTX-B in children, or in patients with known neuromuscular disease or neuromuscular junction disorders. It was added that the risk of toxin spread with botulinum toxins is rare but serious and has been reported with all products in this class.

IV. RAPPORTEUR'S CONCLUSION AND RECOMMENDATION AT DAY 70

The paediatric studies submitted by MAH1 did not provide any new efficacy or safety data. Based on the submitted studies and post marketing safety data submitted by both MAHs, the rapporteur concludes:

- Off label use of BTX-A products continues to occur in children in terms of use below 2 years of age and use in indications other than the licensed one. The extend of off label use is not determined but based on the data submitted and reviewed literature, it seems to be considerable.

- Factors that may contribute to increased risks from BTX-A treatment in children are: off label use, significant disability and comorbidities in children treated, variable dosing regimens, variable dosing frequencies, multiple muscle groups being treated at the same time which may increase the risk of medication errors and overdosage. Furthermore, there is potential confusion amongst clinicians and users with regards to dosing using the two different products which could be an additional risk for patients.

- Overall, the paediatric data submitted by the 2 MAHs confirmed the known safety concerns for BTX-A. All reported AEs are mentioned in the products' SmPCs. No new safety information was identified.

- A significant number of fatal cases are reported. It is acknowledged that the fatal events occurred in patients with underlying severe neuromuscular disorders (CP) which could be associated with common occurrence of oropharyngeal motor problems, recurrent aspirations and respiratory problems. However, as in most of these cases the respiratory deterioration occurred after the injection of BTX-A, a contributory or causal effect of the toxin cannot be excluded based on the narratives provided. Other confounders in assessing causality include increased anaesthetic risk or risk from sedation in these patients.

The potential for distant spread of the toxin with severe systemic effects and rarely death is known for BTX-A products and has been addressed by previous regulatory procedures as mentioned above.

The SmPCs of Dysport and Botox have relevant information in sections 4.4 and 4.8:

- side effects related to toxin distant spread
- the need to use with caution in patients with neurological diseases
- the need to use with caution in patients with swallowing or breathing difficulties as these may worsen following the distribution of the effect of toxin into the relevant muscles. Dysphagia, pneumonopathy, aspiration and even death have occurred in some very rare cases.
- awareness and caution about the rare possibility of distant spread of toxin in paediatric patients with comorbidities, predominantly CP. In general, the dose used in these cases was in excess of that recommended and some cases involved off label use.

- treatment in patients with poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks.

In addition, detailed information about paediatric posology, total maximum dose, intervals between repeated injections and injection guiding techniques are provided in relevant SmPC sections.

Despite this information, the risk may still not be fully appreciated by clinicians. This is of particular concern when botulinum toxin is used in very young children with severe underlying disease in conjunction with anaesthesia; for those patients, which already have limited respiratory reserves, subclinical manifestation of ADRs might mean that they are at risk of late diagnosis of the serious systemic effects of the drug. There is a need for clear clinical guidelines and indeed the product should be used only within the context of appropriate clinical services and with clear and continuous training.

Both MAHs are requested to continue monitoring ADRs in children, both in the licensed indication and during off label use. Serious cases, including fatal cases, should be submitted in detail via the appropriate PV regulatory procedures to ensure identification of potential new safety concerns and signals and if needed, further regulatory actions should be taken.

In conclusion, following this procedure the benefit:risk ratio of botulinum toxin has not changed.

V.COMMENTS FROM MSS AT DAY 85

The rapporteur received comments from 3 MSs: MS1, MS2, MS3. MS1 endorsed the rapporteur's assessment and had no further comments.
MS2 endorsed the rapporteur´s conclusion and supported the request for supplementary information. MS2 highlighted that, besides Dysport, Botox and Neurobloc that are BTX products mentioned in the report, Xeomin is also a BTX product which is not mentioned. Off label use of Xeomin in children cannot be excluded and therefore potential consequences of this worksharing procedure for all licensed BTX products should be considered.

MS3 endorsed the rapporteur assessment but also had additional comments. MS3 proposed "to request both MAHs to further quantify post-marketing patient exposure in children and differentiate this exposure to different age categories as far as possible. From the submitted data, the extent of use in children below the age limits mentioned in the indication could not be established. Therefore, no correlation between use and reported adverse events can be made. This correlation is needed to determine whether additional amendment to the SmPC should be established." This will be added to the request for information.

With regard to Botox, MS3 stated that it is unclear whether the rapporteur is suggesting mentioning the age limit in the indication. If this is indeed the intention, this is not supported as MS3 considers that, based on the data submitted no SmPC change is considered necessary. The rapporteur has not proposed that the age limits for the different Botox indications should be changed. However, according to the SmPC guideline, section 4.1 should state in which age groups the product is indicated, specifying the age limits, and this should be reflected also in section 4.2.

MS3 noted that the submitted data suggest that Dysport is being used in the paediatric population below the age limit mentioned in section 4.1. MS3 proposed to advise the MAH for Dysport to include a warning in SmPC section 4.4 to make physicians more aware of the possible risks:

“The safety and efficacy of <product name> in indications other than those described for the paediatric population in section 4.1 has not been established. Post-marketing reports of possible distant spread of toxin have been very rarely reported in paediatric patients with comorbidities, predominantly with cerebral palsy. In general the dose used in these cases was in excess of that recommended (see section 4.8).
There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin, including following off label use (e.g. neck area). Extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease. Treatment in patients with poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks.”

VI.REQUEST FOR SUPPLEMENTARY INFORMATION AT DAY 89

See questions and MAHs’ responses in the following section VII.

VII. ASSESSMENT OF RESPONSE TO QUESTIONS

1.**The SmPC of Botox has information in section 4.1 and 4.2 that could potentially be misinterpreted with regards to the paediatric licensed indications. MAH2 should review the information included in section 4.1 and 4.2. MAH2 should explain what information the age groups in the table (section 4.2) is referring to and how this information reflects the approved indications, including the age group(s) for which the product is licensed. If needed, the MAH should propose wording for sections 4.1 and 4.2 which is consistent with the licensed paediatric indication(s) and in line with the SmPC guideline.**

MAH2 response:
The MAH has reviewed the information in section 4.1 and 4.2 of the BOTOX SmPC with regards to paediatric licensed indications. The information as described in the table within Section 4.2 refers to the ages below which the safety and efficacy of BOTOX has not been established. This information was previously included in the SmPC in text format and has undergone review and update when each BOTOX indication has been added to the label and has not previously been raised as a concern. As recently as March 2014, the text was amended via Type II Variation (IE/H/0113/001-003/II/86) into a tabulated format for ease of reading. With several labelling variations approved since 2014, no issue has been raised and the MAH has not been made aware of any confusion or misinterpretation of the information provided.
Some of the indications listed in section 4.1 specify that they are for adults, and for those that don’t specify, further information is provided in the table within section 4.2. Please note that Section 4.4 emphasises that “The safety and efficacy of BOTOX in indications other than those described for the paediatric population in section 4.1 has not been established.”
No additional data has been received that would imply a change to the wording in section 4.1 or 4.2 is warranted and as such, to avoid potential for confusion, the MAH proposes that updates to the wording in Section 4.1 and 4.2 are not required at this time and support that the current approved text is in line with the SmPC guideline.

Rapporteur ‘s comments:
The MAH concludes that no changes in the SmPC sections 4.1 and 4.2 are warranted as no issues have been raised in previous regulatory procedures.

However, as the MAH states, some indications listed in section 4.1 specify that they are for adults and for some the age group is not specified; despite this lack of clarity in section 4.1, the MAH supports that the prescriber can find sufficient information about paediatric use and licensed indications in children in other SmPC sections, e.g.in sections 4.2 and 4.4.

Taking into consideration the need for evidence-based paediatric information and the risks, including death, identified for the paediatric population from use of botulinum toxin (including during off label), all information on paediatric use should be clear throughout the SmPC and according to the 2009 SmPC guideline. Therefore, section 4.1 should be updated to clearly state, for every listed indication, in which age groups the product is indicated. However, as indicated by the RMS for this product, no changes in this section can be recommended as part of this European WS procedure under Article 45 since the benefit:risk ratio for Botox has not changed based on the submitted data.

Section 4.2, under the heading “paediatric population” contains information in table format that can be misinterpreted and therefore its appropriateness is challenged. To clarify the current paediatric information in this section, we propose the following:

- For consistency between different SmPC sections, replace the sentence “The safety and efficacy of BOTOX in the treatment of individual indications have not been established in children and adolescents under the ages listed in the table below” with a more clear sentence that already exists in section 4.4 of the SmPC: “The safety and efficacy of BOTOX in indications other than those described for the paediatric population in section 4.1 has not been established.”

- Clarify that there are no posology recommendations for indications other than focal spasticity associated with paediatric cerebral palsy.

- Add that currently available data per indication are described in section 4.2,4.4, 4.8 and 5.1.

- In order to simplify the existing table, remove reference to indications for which no paediatric data are available in the SmPC.

- Clarify for the remaining indications where in the SmPC available paediatric data are available.

The following specific SmPC changes in the wording of section 4.2 are proposed:

Paediatric population

The safety and efficacy of BOTOX ~~in the treatment of individual indications have not been established in children and adolescents under the ages listed in the table below. No data are available.~~ **in indications other than those described for the paediatric population in section 4.1 have not been established. No recommendation on posology can be made for indications other than focal spasticity associated with paediatric cerebral palsy. Currently available data per indication are described in section 4.2,4.4, 4.8 and 5.1 as shown in the table below.**

• Focal spasticity associated with paediatric cerebral palsy	2 years **(see section 4.2, 4.4 and 4.8)**
~~• Upper and lower limb spasticity associated with stroke~~	~~18 years~~
• Blepharospasm/Hemifacial spasm/ Idiopathic Cervical dystonia	12 years **(see section 4.4, 4.8)**

~~• Chronic migraine (CM)~~	~~18 years~~
~~• Overactive Bladder (OAB) and Neurogenic Detrusor Overactivity (NDO)~~	~~18 years~~
• Primary hyperhidrosis of the axillae	12 years (limited experience in adolescents between 12 and 17 years, see sections **4.4,** 4.8 and 5.1)
~~• Glabellar lines seen at maximum frown and/or crow's feet lines seen at maximum smile~~	~~18 years~~

2. **The SmPC of Dysport does not include sufficient information in section 4.4 regarding risk of distant spread of the toxin in children with cerebral palsy and rare reports of severe events and even death in this age group. Per another MSs proposal, text like the one existing in section 4.4 of Botox SmPC should be added in section 4.4 of the Dysport SmPC to make physicians aware of possible risks in children and underline the need to exercise caution when treating patients at higher risk for adverse events. Based on the proposal from NL and with a minor change, the following wording is proposed to be added in section 4.4 of Dysport SmPC:**
"Paediatric use
For the treatment of spasticity associated with cerebral palsy in children, Dysport should only be used in children of 2 years of age or over. Post-marketing reports of possible distant spread of toxin have been very rarely reported in paediatric patients with comorbidities, predominantly with cerebral palsy. In general the dose used in these cases was in excess of that recommended (see section 4.8).
There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin, including following off label use (e.g. neck area). Extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease. Treatment in patients with poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks."

MAH1 response:
The MAH's current wording for section 4.4 includes a warning for the treatment of spasticity associated with cerebral palsy in children; however, it may be further categorised or highlighted as specific to paediatric use as proposed. Therefore, the MAH is in agreement with the proposed wording for section 4.4.

Rapporteur's comments:
MAH1 has agreed to the proposed SmPC changes. Issue resolved.

3. Both MAHs are requested to further quantify post-marketing patient exposure in children and differentiate this exposure to different age categories as far as possible. From the submitted data, the extent of use in children below the age limits mentioned in the indication could not be established. Therefore, no correlation between use and reported adverse events can be made. This correlation is needed to determine whether additional amendment to the SmPC is warranted.

MAH1:
It is not possible to determine the patient exposure from the sales volumes for the paediatric population as the same product is used for the adult population. Exposure data per paediatric age group are therefore not available.

A further analysis per age group was carried out on the 307 post-marketing cases of use in paediatric population (i.e. 159 cases reporting labelled (145) or unknown indications (14) and 148 cases reporting off-label use). The 14 cases that did not report an indication were assumed as use within the label for the purpose of this analysis. This analysis was performed in accordance with the MAH's usual data handling conventions up until 31st March 2017.
Table 1 below presents the on-label use per age group. There were a total of 17 Adolescent, 130 Child and 12 cases where the age group was not reported (i.e. solely reported as paediatric) on-label use cases. In this group it was assumed that the patients were at least 2 years old as there were no indicators to the contrary and the majority (10) of which come from a market research survey/ patient data collecting system.

Table 1: on-label use per age group

Age group	Number of cases	Total adverse events
Adolescent (12-17 years)	17	29
Child (2-11 years)	130	210
Not reported	12	13
Grand Total	**159**	**252**

As per Company Core Safety Information (CCSI), Dysport is licenced for the symptomatic treatment of lower limb focal spasticity in children aged 2 years age or older and the cases in Table 1 relate to this indication. There were a total of 17 cases in the adolescent age corresponding to 29 total adverse events. The most common adverse events in this population were asthenia (4 reports) and muscle weakness (3 reports) with other adverse events occurring in lower numbers. In the child population there were a total of 130 cases corresponding to 210 adverse events reported. The most common of which were asthenia (17 reports), muscle weakness (16 reports) and urinary incontinence (13 cases). These are common adverse reactions and are in line with the known safety profile for this indication.
There were also 15 reports of eyelid ptosis; 6 of which were assessed as possible remote spread with the others being confounded by alternative aetiology and 2 of which had an unspecified indication. In the 12 paediatric cases where the age was not reported, the most reported adverse event was product use issue (8) which is the PT code applied to the use of the product in paediatric lower limb focal spasticity in countries where this indication was not licenced (i.e. drug use in unapproved population as per local SmPC). These were considered on-label in the parameters of this analysis as treatment of lower limb spasticity in children is a licenced indication in a number of European countries. Other adverse events included fatigue (1) and influenza like illness (1) among others.
The adverse events in the adolescent and child age groups are in line with the ADRs i.e. asthenia, muscle weakness and urinary incontinence mentioned in the currently approved SmPC. Additionally, the warning of the possibility of the spread of the toxin is already in the approved SmPC and cases within the database are monitored by routine assessment.

Table 2 below presents the type of off-label use per age group. There were a total of 47 Adolescent, 89 Child, 11 Infant and 1 Neonate off-label use cases. Note that some of these cases were in patients who were injected in both labelled and off-label indications; however, these are presented only once, in the off-label discussion below.

Table 2: off-label use per age group

Age group	Number of cases	Total adverse events
Adolescent	47	105
Child	89	175
Infant (2-23 months)	11	14
Neonate (0-1 month)	1	2

Grand Total	**148**	**296**

The most common type of off-label use in adolescents was hyperhidrosis (13 cases) with the most common adverse event experienced being a lack of efficacy with drug effect decreased and drug ineffective reported 5 and 3 times, respectively. The second most common type of off-label use was upper limb spasticity (8 cases) with several adverse events reported at low frequency including asthenia and dysphagia which are listed events for the approve indication in adults.
Sialorrhea (18 cases) and upper limb spasticity (17 cases) were the most common off-label use in the child age group. There were 12 reports of dysphagia reported in the sialorrhea off label use. Several adverse events were reported at low frequency for upper limb spasticity.
There were 5 instances of eyelid ptosis reported in the ophthalmology off-label use in the child age group. Eyelid ptosis is a common adverse reaction of botulinum type A toxin (BTX-A) when injected in muscles of or near to the face/eye in patients treated for blepharospasm and cervical dystonia. There were a total of 11 Infant cases with 14 adverse events reported, each event being reported only once. 3 cases were reported for an unknown indication.
There was only one neonate case which was an exposure during pregnancy case with a premature birth from the Swiss Health Authority. The mother was exposed to Dysport 67.5 units approximately one week before conception and 10 units approximately 10 days after conception for an unknown indication. The low dose given to the mother of the patient is unlikely to have caused premature delivery but the case was cautiously assessed as related. Given the low number of cases it is difficult to discern any clear pattern in the use of Dysport in paediatric age groups. Most adverse events are reported at low frequency and there are more cases in the adolescent and child age groups than the infant and neonate which is to be expected given the approval for children above the age of 2 in lower limb focal spasticity. Given the limited data, no clear correlation between use in the paediatric population and reported adverse events can be made. The MAH concluded that current data does not warrant any additional amendment to the SmPC.

MAH2:
Although it is not possible to further quantify post-marketing patient exposure to BOTOX by paediatric age group, a crude correlation of the extent of use of BOTOX and reported adverse events by paediatric age group can be determined by examining the distribution of the patients by age in the case reports received to date.
The table below presents the distribution of all fatal, serious, and non-serious paediatric case reports by age group and reported indication received for BOTOX from 01-January-1990 through 31-October-2015.
In this table, the indication preferred terms is summarised under “Authorised Therapeutic Indications (Regardless of Patient Age)” or under off label indications.
The safety information available for paediatric patients <2 years of age for authorised indications (25 total case reports) is limited compared to children (657 total case reports) and adolescents (273 total case reports). Based on this information, it is the MAH’s opinion that no additional amendment to the SmPC is warranted.

Indication PT	No. of Case Reports by Paediatric Age Group and Case Seriousness																Grand Total
	Neonate (birth to <27 days)[a]			Infant (≥28 days to <2 years)				Child (≥2 to ≤12 years)				Adolescent (≥12 to ≤18 years)				
	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	
Authorised Therapeutic Indications (Regardless of Patient Age)																
Blepharospasm	0	1	**1**	0	0	0	**0**	0	0	1	**1**	0	0	2	**2**	4
Cerebral palsy	0	0	**0**	0	1	2	**3**	6	50	86	**142**	1	12	21	**34**	179
Congenital torticollis	0	0	**0**	0	0	1	**1**	0	0	2	**2**	0	0	1	**1**	4
Dystonia	0	0	**0**	0	0	0	**0**	0	2	1	**3**	0	2	3	**5**	8
Facial spasm	0	3	**3**	0	0	0	**0**	0	0	0	**0**	0	0	1	**1**	4
Hyperhidrosis	0	0	**0**	0	0	0	**0**	0	0	2	**2**	0	6	94	**100**	102
Hypertonic bladder	0	0	**0**	0	0	0	**0**	0	4	19	**23**	0	1	0	**1**	24
Migraine	0	0	**0**	0	0	0	**0**	0	0	6	**6**	0	2	15	**17**	23
Muscle spasms	0	0	**0**	0	0	0	**0**	1	10	8	**19**	2	1	6	**9**	28
Muscle spasticity	0	0	**0**	1	2	7	**10**	18	122	172	**312**	7	31	34	**72**	394
Neurogenic bladder	0	0	**0**	0	0	0	**0**	0	8	18	**26**	0	3	2	**5**	31
Torticollis	0	0	**0**	2	1	8	**11**	15	27	79	**121**	5	11	10	**26**	158
Subtotal	0	4	4	3	4	18	25	40	223	394	657	15	69	189	273	959
Off-Label Indications																
Aicardi's syndrome	0	0	**0**	0	0	0	**0**	0	1	0	**1**	0	0	0	**0**	1
Alopecia areata	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	2	**2**	3
Anal fissure	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Anal spasm	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Anal sphincter atony	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	1	0	**1**	1
Anal sphincter hypertonia	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Arthropathy	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	0	1	**1**	1
Automatic bladder	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	1	0	**1**	1
Back pain	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	1	0	**1**	1
Basilar migraine	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	0	1	**1**	1
Bladder disorder	0	0	**0**	0	0	0	**0**	0	0	5	**5**	0	0	0	**0**	5
Bladder fibrosis	0	0	**0**	0	0	0	**0**	0	0	2	**2**	0	0	0	**0**	2

Indication PT	No. of Case Reports by Paediatric Age Group and Case Seriousness																Grand Total
	Neonate (birth to <27 days)[a]			Infant (≥28 days to <2 years)				Child (≥2 to ≤12 years)				Adolescent (≥12 to ≤18 years)				
	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	
Brain injury	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Brain stem syndrome	0	1	**1**	0	0	0	**0**	0	0	0	**0**	0	0	0	**0**	1
Bruxism	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	1	0	**1**	2
Congenital megacolon	0	0	**0**	0	1	0	**1**	0	0	0	**0**	0	0	0	**0**	1
Constipation	0	0	**0**	0	0	0	**0**	0	0	2	**2**	0	0	0	**0**	2
Cranial nerve paralysis	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Dacryostenosis acquired	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Diplegia	0	0	**0**	0	0	0	**0**	0	6	8	**14**	0	1	0	**1**	15
Drooling	0	0	**0**	0	0	0	**0**	1	8	21	**30**	0	5	2	**7**	37
Drug administered at inappropriate site	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	0	1	**1**	1
Duane's syndrome	0	0	**0**	0	0	2	**2**	0	0	1	**1**	0	0	0	**0**	3
Dysuria	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Enterocolitis	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Essential tremor	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Exposure during breast feeding	0	0	**0**	0	0	5	**5**	0	0	3	**3**	0	0	0	**0**	8
Exposure during pregnancy	1	0	**1**	0	0	0	**0**	0	0	0	**0**	0	0	0	**0**	1
Eyelid ptosis	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	0	1	**1**	1
Eye movement disorder	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	0	1	**1**	1
Foetal exposure during pregnancy	0	0	**0**	0	1	0	**1**	0	0	0	**0**	0	0	0	**0**	1
Foot deformity	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Gait disturbance	0	0	**0**	0	0	0	**0**	0	1	0	**1**	0	1	0	**1**	2
Gastrointestinal obstruction	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1

Indication PT	No. of Case Reports by Paediatric Age Group and Case Seriousness																Grand Total
	Neonate (birth to <27 days)[a]			Infant (≥28 days to <2 years)				Child (≥2 to ≤12 years)				Adolescent (≥12 to ≤18 years)				
	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	
Headache	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	4	**4**	5
Hemiparesis	0	0	**0**	0	0	0	**0**	0	2	1	**3**	0	0	2	**2**	5
Hemiplegia	0	0	**0**	0	1	1	**2**	0	0	2	**2**	0	0	0	**0**	4
Hypertonia	0	0	**0**	0	0	0	**0**	0	2	0	**2**	0	0	1	**1**	3
Joint contracture	0	0	**0**	0	0	0	**0**	0	1	0	**1**	0	0	0	**0**	1
Lacrimation increased	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Leukodystrophy	0	0	**0**	0	0	0	**0**	0	1	0	**1**	0	0	0	**0**	1
Maternal exposure during pregnancy	1	0	**1**	0	2	1	**3**	0	0	0	**0**	0	0	0	**0**	4
Maternal exposure timing unspecified	7	2	**9**	0	1	1	**2**	0	1	0	**1**	0	0	0	**0**	12
Meningoencephalitis herpetic	0	0	**0**	0	0	0	**0**	1	0	0	**1**	0	0	0	**0**	1
Meningomyelocele	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	1	**1**	2
Micturition disorder	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Movement disorder	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	1	0	**1**	1
Mucopolysaccharidosis IV	0	0	**0**	0	0	0	**0**	0	1	0	**1**	0	0	0	**0**	1
Muscle contracture	0	0	**0**	0	1	0	**1**	0	1	0	**1**	0	0	1	**1**	3
Muscle disorder	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	0	2	**2**	2
Muscle tightness	0	0	**0**	0	0	1	**1**	1	0	1	**2**	0	1	0	**1**	4
Musculoskeletal disorder	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	1	**1**	2
Myelitis transverse	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Myoclonus	0	0	**0**	0	0	0	**0**	0	1	1	**2**	0	0	1	**1**	3
Nervous system disorder	0	0	**0**	0	0	0	**0**	0	1	0	**1**	0	0	0	**0**	1
Neuralgia	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	0	1	**1**	1

Indication PT	No. of Case Reports by Paediatric Age Group and Case Seriousness																Grand Total
	Neonate (birth to <27 days)[a]			Infant (≥28 days to <2 years)				Child (≥2 to ≤12 years)				Adolescent (≥12 to ≤18 years)				
	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	
Nystagmus	0	0	**0**	0	0	0	**0**	0	1	1	**2**	0	0	0	**0**	2
Oesophageal achalasia	0	0	**0**	0	2	1	**3**	0	1	0	**1**	0	0	1	**1**	5
Ophthalmoplegia	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	0	1	**1**	1
Opisthotonus	0	0	**0**	0	0	0	**0**	0	1	0	**1**	0	0	0	**0**	1
Oromandibular dystonia	0	0	**0**	0	0	1	**1**	0	0	0	**0**	0	0	0	**0**	1
Osteochondrosis	0	0	**0**	0	0	0	**0**	0	1	0	**1**	0	0	0	**0**	1
Pain	0	0	**0**	0	0	0	**0**	0	0	0	**0**	1	1	1	**3**	3
Paralysis	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	1	**1**	2
Paraparesis	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Paraplegia	0	0	**0**	0	0	0	**0**	0	0	2	**2**	0	0	0	**0**	2
Paresis	0	0	**0**	0	0	0	**0**	0	1	0	**1**	0	1	0	**1**	2
Phantom pain	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	0	1	**1**	1
Positional plagiocephaly	0	0	**0**	0	0	1	**1**	0	0	0	**0**	0	0	0	**0**	1
Product used for unknown indication	0	0	**0**	0	2	1	**3**	4	7	44	**55**	1	6	13	**20**	78
Quadriparesis	0	0	**0**	0	0	0	**0**	0	2	0	**2**	0	0	0	**0**	2
Quadriplegia	0	0	**0**	0	0	0	**0**	2	2	2	**6**	0	1	2	**3**	9
Rhinalgia	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	0	1	**1**	1
Salivary gland disorder	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Salivary hypersecretion	0	0	**0**	0	1	0	**1**	0	14	15	**29**	0	5	1	**6**	36
Scoliosis	0	0	**0**	0	0	0	**0**	1	0	7	**8**	1	2	1	**4**	12
Secretion discharge	0	0	**0**	0	0	0	**0**	0	1	0	**1**	0	0	0	**0**	1
Skin wrinkling	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	0	3	**3**	3
Somatic symptom disorder	0	0	**0**	0	0	2	**2**	0	0	0	**0**	0	0	0	**0**	2
Spinal muscular atrophy	0	0	**0**	0	0	0	**0**	0	1	0	**1**	0	0	0	**0**	1
Strabismus	0	0	**0**	0	2	3	**5**	0	7	44	**51**	0	1	0	**1**	57

Indication PT	No. of Case Reports by Paediatric Age Group and Case Seriousness															
	Neonate (birth to <27 days)[a]			Infant (≥28 days to <2 years)				Child (≥2 to ≤12 years)				Adolescent (≥12 to ≤18 years)				Grand Total
	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	Fatal	Serious	Non-Serious	Total	
Talipes	0	0	**0**	0	1	1	**2**	0	1	1	**2**	0	0	0	**0**	4
Therapeutic procedure	0	0	**0**	0	0	3	**3**	0	0	0	**0**	0	0	0	**0**	3
Therapeutic product ineffective	0	0	**0**	0	0	0	**0**	0	0	1	**1**	0	0	0	**0**	1
Tic	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	1	0	**1**	1
Toe walking	0	0	**0**	0	0	0	**0**	0	0	4	**4**	0	0	0	**0**	4
Tourette's disorder	0	0	**0**	0	0	0	**0**	0	0	0	**0**	0	1	0	**1**	1
Tremor	0	0	**0**	0	0	0	**0**	1	0	0	**1**	0	0	0	**0**	1
Urinary incontinence	0	0	**0**	0	0	0	**0**	0	2	0	**2**	0	3	0	**3**	5
Urinary retention	0	0	**0**	0	0	0	**0**	0	0	3	**3**	0	0	0	**0**	3
Subtotal	9	3	12	0	15	24	39	11	69	193	273	3	35	49	87	411
Grand Total	**9**	**7**	**16**	**3**	**19**	**42**	**64**	**51**	**292**	**587**	**930**	**18**	**104**	**238**	**360**	**1,370[b]**

[a] Neonates (birth to <27 days old) were exposed to BOTOX during gestation or breast feeding.

[b] The grand total is greater than the total number of case reports (1276) because a case report can include multiple indications for the use of BOTOX.

Rapporteur's comments:
Both MAHs could not provide data to further quantify post-marketing patient exposure to Botox in children. However, the MAHs submitted data from reported AEs by paediatric age group and MAH2 also by indication.
It is noted that MAH2 considers as licensed indications any indication in any age group, adults or children, and not only those approved in children. This is confusing as, similarly to the SmPC for Botox, the paediatric licensed indications are not clarified.

From the data submitted it is concluded that Botox is used in children of any age in a variety of indications, spanning various symptoms and conditions mainly of the nervous system.
Based on the data provided, the extent of use, including off label use, in children could not be established. However, based on the reported adverse events and their categorisation per indication, it is clear that off label use, both in terms of indication and paediatric age group, is substantial.
Therefore, it is even more important that SmPC information on licensed indications in the paediatric population as well as safety information about risks from BTX use are clear.

4. Both MAHs are requested to confirm that all identified serious and fatal paediatric cases have been reviewed through the appropriate PV regulatory procedures (PSURs). The MAHs should conclude, based on review of all safety information, if, further regulatory actions should be considered following the conclusion of this European work-sharing procedure under Article 45.

MAH1:
All paediatric cases including serious and fatal cases are systematically reviewed in the scheduled PSURs in section 16.4.3.2 "Use in Children". Review of the cases did not indicate a safety issue for use in this patient population and did not identify any information that alters the benefit risk assessment of the product or that would warrant any changes to current risk minimisation measures i.e. product labelling. Routine pharmacovigilance processes for botulinum type A toxin-haemagglutinin complex (BTX-A-HAC) include regular signal detection activities such as ICSR review from all sources (including the published literature, clinical trials and postmarketing sources) and review of disproportionate reporting data using standard statistical thresholds plus review of line listings to identify any typical drug reactions of medical and regulatory importance. This process would capture any alerts that may impact the safety profile and is well defined. There is no suggestion that further actions are warranted.

MAH2:
The MAH confirms that all identified serious and fatal paediatric case reports that met PSUR reporting criteria have been reviewed and reported in PSURs.

Of note, the rapporteur's comments in the Day 89 Assessment Report for this Article 45 procedure regarding a cumulative review (01 January 1990-30 June 2011) of adverse events in the indication of torticollis, included the following statement (page 31):
"A total of 19 cases reported a fatal outcome, of which all but one was reported from Japan. 15/19 cases were received from a non-interventional active post-marketing surveillance program conducted in Japan (a mandatory regulatory authority requirement in Japan for all products). No other details for this surveillance program are provided, i.e. the period it covered and the number of children being treated during that period. Nevertheless, 19 fatal cases is a large number despite the MAH's statement that the majority of the serious and fatal cases were unrelated to Botox treatment. As no case details are presented here, potential association between the fatal outcome and Botox treatment cannot be excluded."
The MAH verifies that these 19 fatal case reports in the special safety analysis for the indication of paediatric torticollis were reviewed and reported also with the interval data for their respective PSURs. In addition, the following special safety analyses reviewed and reported all targeted case reports, including those that did not meet PSUR criteria (except as noted):

- Cumulative analysis (01-January-1990 to 31-May-2008) of all fatal and serious paediatric case reports, presented in PSUR #15 (this analysis was requested by the IMB and AFFSAPs).
- Cumulative analyses (01-January-1990 to 30-June-2011) of all case reports for the indication of paediatric torticollis (which included such case reports from the GSK Japanese post-marketing surveillance study), fatal and serious case reports for the indication of paediatric muscle spasticity (excluding cases from sponsored clinical trials), and all case reports involving the use of sedation anaesthesia in paediatric patients; these 3 analyses were presented in PSUR #20.
- Interval analysis (01-January-2012 to 31-December-2012) of all paediatric case reports, presented in PSUR #21 (this analysis was undertaken as requested in the Assessment Report for PSUR #20).
- Interval analyses of all fatal and serious paediatric case reports involving off-label usage and higher than recommended maximum dose, for the periods 01-January-2012 to 31-December-2012 (presented in PSUR #21), 01-January-2013 to 31-October-2013 (presented in PSUR #22), and 01- January-2013 to 31-October-2015 (presented in PSUR #24) (this analysis was undertaken as requested in the Assessment Reports for PSURs #20 and #21).

It is the MAH's opinion that the risk-benefit of botulinum toxin type A has not changed and no further regulatory actions should be considered following the conclusion of this European work-sharing procedure under Article 45.
The MAH will continue to monitor the safety profile of BOTOX in paediatric patients, both in licensed indications and off-label use, and collect adequate case details to allow assessment of potential causality between botulinum toxin type A treatment and adverse events (AEs) and any association with specific indications, dosage and dosage intervals used, different age groups, and underlying conditions. Serious cases, including fatal cases, will continue to be submitted in detail via the appropriate PV regulatory procedures to ensure identification of potential new safety concerns and signals and, if needed, further regulatory actions.

Rapporteur's comments:

Both MAHs have confirmed that all identified serious and fatal paediatric cases have been reviewed through the appropriate PV regulatory procedures. In addition, the MAHs confirmed that no further regulatory actions are warranted following the conclusion of this work-sharing procedure under Article 45. Issue resolved.

VIII. COMMENTS FROM MSS AT DAY 115

3 MSs provided comments:
MS2 agreed with the rapporteur's AR and with the changes in SmPC in section 4.4 in Dysport and section 4.2 in Botox.

MS3: Data are available for the use of Botox in blepharospasm, hemifacial spasm, idiopathic cervical dystonia and primary hyperhidrosis of the axillae in children aged 12 years and older. This is clarified by adding the age limit 2 to 12 years old. Therefore, MS3 proposes a change to the wording in section 4.2 of the SmPC for Botox (see bold, blue underlined text):

Paediatric population
The safety and efficacy of BOTOX ~~in the treatment of individual indications have not been established in children and adolescents under the ages listed in the table below. No data are available.~~ in indications other than those described for the paediatric population in section 4.1 have not been established. No recommendation on posology **in children aged 2 to 12 years old** can be made for indications other than focal spasticity associated with paediatric cerebral palsy. Currently available data per indication are described in section 4.2,4.4, 4.8 and 5.1 as shown in the table below.

MS4 agreed with the rapporteur's conclusion but proposed the following revision to the proposed text for section 4.2.

Section 4.2:

Paediatric population

The safety and efficacy of BOTOX in the treatment of individual indications have not been established in children and adolescents under the ages listed in the table below ~~**in indications other than those described for the paediatric population in section 4.1 have not been established.**~~ **No recommendation on posology can be made for indications other than focal spasticity associated with paediatric cerebral palsy. Currently available data per indication are described in section 4.2,4.4, 4.8 and 5.1 as shown in the table below.**

• Focal spasticity associated with paediatric cerebral palsy	2 years **(see section 4.2, 4.4 and 4.8)**
~~• Upper and lower limb spasticity associated with stroke~~	~~18 years~~
• Blepharospasm/Hemifacial spasm/ Idiopathic Cervical dystonia	12 years **(see section 4.4, 4.8)**
~~• Chronic migraine (CM)~~	~~18 years~~
~~• Overactive Bladder (OAB) and Neurogenic Detrusor Overactivity (NDO)~~	~~18 years~~
• Primary hyperhidrosis of the axillae	12 years

	(limited experience in adolescents between 12 and 17 years, see sections **4.4,** 4.8 and 5.1)

Rapporteur's comments:
MS3 proposed to specify that posology recommendations cannot be given for children 2-12 years in indications other than focal spasticity based on available data in children above 12 years in these indications. However, there is no posology recommendation in any age group in the SmPC for these other indications. Available paediatric data in other indications exist in other sections of the SmPC but not in section 4.2. Therefore, we do not agree with this addition.

MS4 proposed to maintain the first sentence in section 4.2 as it is currently in the SmPC: "*The safety and efficacy of Botox in the treatment of individual indications have not been established in children and adolescents under the ages listed in the table below."*
The rapporteur concludes that in an effort to reduce the ambiguity of paediatric information in section 4.2, the sentence "The safety and efficacy of BOTOX in indications other than those described for the paediatric population in section 4.1 has not been established" is preferable and this change was also supported by MS3 and MS2.

IX. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Based on the submitted studies and postmarketing safety data submitted by both MAHs, the rapporteur concludes that the benefit:risk ratio of botulinum toxin has not changed for the licensed paediatric indication.
Both MAHs are requested to continue monitoring ADRs in children, both in the licensed indication and during off label use. Serious cases, including fatal cases, should be submitted in detail via the appropriate PV regulatory procedures to ensure identification of potential new safety concerns and signals and if needed, further regulatory actions should be taken.

Taking into consideration the substantial off label use of BTX-A in children and identified risks, including death, from such use, it is important that prescribing paediatric information in the SmPC of BTX products is clear.

For Dysport, SmPC changes have been proposed by the rapporteur and accepted by the MAH to strengthen the information in section 4.4 about potential risks from BTX-A treatment in children.

For Botox, the rapporteur concludes that information included in section 4.1 and 4.2 regarding paediatric indications and available paediatric data is not clear. However, as it is not within the remit of article 45 to change the licensed indications without the submission of new paediatric data, no changes in section 4.1 are proposed. For section 4.2 of the Botox SmPC, wording is proposed to clarify the existing SmPC paediatric information and maintain consistency of wording in different sections of the SmPC.
Following circulation of the final report, MAH2 proposed some minor formatting amendments to the SmPC wording which are acceptable. Specifically, the MAH proposed that the indications "*Blepharospasm/Hemifacial spasm*" and "*Cervical dystonia*" are mentioned separately as these are listed as separate indications in section 4.1.

The following SmPC changes are proposed (new text in bold and underlined):

Dysport:

Section 4.4:

Paediatric use
For the treatment of spasticity associated with cerebral palsy in children, Dysport should only be used in children of 2 years of age or over. Post-marketing reports of possible distant spread of toxin have been very rarely reported in paediatric patients with comorbidities, predominantly with cerebral palsy. In general the dose used in these cases was in excess of that recommended (see section 4.8).
There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin, including following off label use (e.g. neck area). Extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease. Treatment in patients with poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks.

Botox:

Section 4.2:

Paediatric population

The safety and efficacy of BOTOX ~~in the treatment of individual indications have not been established in children and adolescents under the ages listed in the table below. No data are available.~~ **in indications other than those described for the paediatric population in section 4.1 have not been established. No recommendation on posology can be made for indications other than focal spasticity associated with paediatric cerebral palsy. Currently available data per indication are described in section 4.2,4.4, 4.8 and 5.1 as shown in the table below.**

• Focal spasticity associated with paediatric cerebral palsy	2 years **(see section 4.2, 4.4 and 4.8)**
~~• Upper and lower limb spasticity associated with stroke~~	~~18 years~~
• Blepharospasm/Hemifacial spasm	12 years **(see section 4.4, 4.8)**
• Cervical dystonia	12 years **(see section 4.4, 4.8)**
~~• Chronic migraine (CM)~~	~~18 years~~
~~• Overactive Bladder (OAB) and Neurogenic Detrusor Overactivity (NDO)~~	~~18 years~~
• Primary hyperhidrosis of the axillae	12 years (limited experience in adolescents between 12 and 17 years, see sections **4.4,** 4.8 and 5.1)

The MAHs should submit a Type IB variation in order to add the SmPC text agreed during the paediatric assessment procedure within 60 days of publication of the public assessment report.

X.LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Product name	Active Substance	MAH
BOTOX 100 Allergan units - Powder for solution for injection	BOTULINUM TOXOID TYPE A	ALLERGAN LIMITED
BOTOX 50 Allergan units - Powder for solution for injection	BOTULINUM TOXOID TYPE A	ALLERGAN LIMITED
BOTOX 200 Allergan units - Powder for solution for injection	BOTULINUM TOXOID TYPE A	ALLERGAN LIMITED
VISTABEL, 4 Allergan Units/0.1ml, powder for solution for injection	BOTULINUM TOXOID TYPE A	ALLERGAN PHARMACEUTICALS IRELAND
Dysport 300 units Powder for solution for injection	CLOSTRIDIUM BOTULINUM TYPE A TOXIN - HAEMAGGLUTININ COMPLEX	IPSEN LIMITED
Dysport 500 units Powder for solution for injection	CLOSTRIDIUM BOTULINUM TYPE A TOXIN - HAEMAGGLUTININ COMPLEX	IPSEN LIMITED
Botulinum Toxin Type A 300 units powder for solution for injection	CLOSTRIDIUM BOTULINUM TYPE A TOXIN - HAEMAGGLUTININ COMPLEX	IPSEN LIMITED
Botulinum Toxin Type A 500 units powder for solution for injection	CLOSTRIDIUM BOTULINUM TYPE A TOXIN - HAEMAGGLUTININ COMPLEX	IPSEN LIMITED