AWMSG Secretariat Assessment Report – Limited submission

Clostridium botulinum type A toxin-haemagglutinin complex (Dysport®) 300 units and 500 units powder for solution for injection

Company: Ipsen Limited

Licensed indication under consideration: Symptomatic treatment of focal spasticity of upper limbs in paediatric cerebral palsy patients, two years of age or older.

Date of licence extension: 17 December 2019

Comparator(s)

- Off-label Botulinum toxin type A (Botox®)

Limited submission details

- Use of botulinum toxin type A for the indication under consideration is recognised as established practice and is recommended in NICE clinical guidelines. Dysport® is the first botulinum toxin type A product to be specifically licensed for the symptomatic treatment of focal spasticity of upper limbs in paediatric cerebral palsy patients, two years of age or older.
- Anticipated usage in NHS Wales is considered to be of minimal budgetary impact.

Clinical effectiveness

- Dysport® contains botulinum toxin type A, derived from the bacterium *Clostridium botulinum*. The toxin inhibits the release of acetylcholine, which acts between nerves and muscles to make the muscle contract, thereby helping to relieve muscle spasms. For the indication covered by this submission, Dysport® is injected into the affected muscles in the arms. Dosage is tailored to the individual patient and depends on a number of factors, such as the size, number and location of muscles involved and the severity of spasticity. Treatment is repeated as needed, when the effect of the previous injection has worn off; the minimum period between treatment sessions in the Dysport® marketing authorisation is 16 weeks.
- NICE Clinical Guideline 145 (Spasticity in under 19s: management) recommends that treatment with botulinum toxin type A be considered in children and young people where focal spasticity of the upper limb is impeding fine motor function, compromising care and hygiene, causing pain, impeding tolerance of other treatment (e.g. orthoses) or causing cosmetic concerns to the individual. This guideline was published before

Clinical effectiveness

Dysport® was licensed for the treatment of focal spasticity of the upper limb and does not specify which botulinum toxin type A preparation to use. Clinical expert opinion sought by AWTTC confirms that Botox® is currently the established botulinum type A toxin treatment for this indication in Wales. Welsh clinical experts indicated more flexibility with Botox® dosing and administration due to the variety of vial sizes available. Doses for botulinum preparations are product specific and are not interchangeable.

- The company submission includes results from one phase III multicentre randomised, double-blind, controlled study that compared doses of 8 U/kg and 16 U/kg Dysport® with an active control arm which received 2 U/kg Dysport®. The use of a placebo was considered unethical because injection into the upper limb muscles in children often requires anaesthesia or sedation. Children aged 2 to 17 years with cerebral palsy and increased muscle tone/spasticity in at least one upper limb and a Modified Ashworth Scale (MAS) score (see Glossary) ≥ 2 in the primary targeted muscle group (PTMG; elbow or wrist flexors) were included. A total of 210 children were randomised and received treatment. The total dose for the selected upper limb was divided across the PTMG and other upper limb muscles, the latter determined by clinical presentation. Treatment was administered in addition to a personalised, goal-oriented home exercise therapy programme, with a minimum expected requirement of five 15-minute sessions per week. Up to four treatment cycles were allowed over a minimum period of one year, with at least 16 weeks between each treatment cycle. In treatment cycles 2 to 4, patients who had initially received the 2 U/kg dose were randomised to receive 8 U/kg or 16 U/kg.
- The primary endpoint was the mean change from baseline in the MAS score in the PTMG at week 6. There was a statistically significant improvement (reduction) in MAS score for the 8 U/kg and 16 U/kg doses compared with the 2 U/kg control group at week 6. At week 16, the change from baseline in the MAS score in the PTMG was lower in all three groups than at week 6, but was statistically significantly better in the 8 U/kg and 16 U/kg groups than the 2 U/kg group. Results for the secondary endpoints, mean Physician Global Assessment (PGA) score (see Glossary) and mean Goal Attainment Scale (GAS) score (see Glossary) at week 6 showed clinically relevant improvements in all three groups, but no statistically significant differences between the groups. Use of the 2 U/kg control arm in the study may have led to a greater treatment effect than if a placebo control arm had been used.
- Efficacy was generally maintained during treatment cycles 2 to 4, as measured by MAS in the PTMG, PGA score and GAS total score at week 6 after each retreatment, and similar between the 8 U/kg and 16 U/kg groups.
- The mean time to retreatment in cycle 1 was approximately 22, 24 and 26 weeks for the 2 U/kg, 8 U/kg and 16 U/kg doses, respectively. Between 60% and 65% of children (across all groups) were retreated between weeks 16 and 28, with almost a quarter not requiring retreatment until 34 weeks or later (19%, 25% and 24% for the 2 U/kg, 8 U/kg and 16 U/kg doses, respectively). In cycles 2 and 3 the mean time to retreatment was

Clinical effectiveness

approximately 19 weeks and 17 weeks, respectively (combined data for the 8 U/kg and 16 U/kg doses).

- Quality of life was measured at week 16 of each treatment cycle using a cerebral palsy-specific module of the Paediatric Quality of Life™ tool (PedsQL™). Except in two subscales (fatigue; movement and balance), no statistically significant improvements were observed.
- In the absence of head-to-head trials between Dysport® and Botox®, the company submission included comparative efficacy through an indirect treatment comparison (ITC). Although point estimates were in favour of Dysport® for most efficacy outcomes, the results did not show a statistically significant difference between treatments. Results of the ITC should be interpreted with caution due to low sample size and number of eligible studies, differences in study design and variability in the timing of outcome assessments. Additionally, a key assumption for the ITC was that the 2 U/kg control arm used for Dysport® was equivalent to placebo.
- Safety data from the phase III study described above combined with safety data from 21 children treated with Dysport® for spasticity in lower and upper limbs in a phase III open-label study and global post marketing safety data did not identify any new safety concerns. Results of the ITC did not show any statistical difference in safety outcomes between Dysport® and Botox®.
- Dysport® should only be administered by an appropriately qualified healthcare practitioner with expertise in treating upper limb spasticity in children with cerebral palsy and use of the necessary equipment (the use of injection guiding technique, e.g. electromyography, electrical stimulation or ultrasound, is recommended to target the injection sites).

Budget impact

- The company estimates 501 children in Wales with cerebral palsy aged 2 years and older to be eligible for treatment with Dysport® each year for the indication covered in this submission. This estimate is based on paediatric population data for Wales and prevalence data for cerebral palsy in the UK and proportion of patients with upper limb spasticity treated with botulinum type A toxin.
- The budget impact analysis assumes that in a market without Dysport®, that all eligible patients are treated with Botox®. The company estimates that 251 children in Year 1 and 426 children in Year 5 will receive Dysport®, based on an estimated market share of 50% in Year 1 increasing to 85% in Year 5. Costs in the base case analysis are calculated using the maximum licensed single upper limb dose of Dysport® (UK) and maximum licensed total dose of Botox® (US) administered per treatment session in the upper limb, and a mean weight (32.4 kg) and administration frequency (25.6 weeks) for both products, taken from the phase III study described above. This results in a net budget impact saving of £46,610 in Year 1 increasing to a saving of £79,237 in Year 5. Resource costs are assumed to be the same for Dysport® and Botox®.

Budget impact

- The company has conducted a significant number of analyses, varying the dose and administration frequency of Dysport® and Botox®, patient weight, number of eligible patients and the cost of Botox®. Dysport® is cost saving in all but one of their scenarios. However, the company estimated cost savings may not be realised in practice as costs and dosing for Botox® and Dysport® vary depending on the patient's weight, vial size used, the number and location of muscles involved and if upper and lower limbs treatments are scheduled in combination.
- The overall budgetary impact is subject to uncertainty but is anticipated to be minimal.

Evidence search

Date of evidence search: 27 September 2021
Date of range of evidence search: No date limits were applied to database searches.

Additional information

- AWTTC is of the opinion that, if recommended, *Clostridium botulinum* toxin-haemagglutinin type A (Dysport®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. *Clostridium botulinum* toxin-haemagglutinin type A (Dysport®) 300 units and 500 units powder for solution for injection. Reference number: 2626. January 2022.

Glossary

Modified Ashworth Scale (MAS)
A clinical scale used to grade muscle tone. Grades range from 0 (no increase in muscle tone) to 4 (affected part[s] rigid in flexion or extension).

Physician Global Assessment (PGA)
A nine-point scale rating the global response from −4 (markedly worse) to +4 (markedly improved), assessed by a different assessor to the MAS.

Goal Attainment Scale (GAS)
A functional scale used to measure progress towards individual therapy goals, defined for each participant before treatment.