Purified botulinum toxin type A (Botox) for post-stroke lower limb spasticity

SUMMARY

Botulinum toxin type A is intended to be used as therapy for the treatment of post-stroke lower limb spasticity. If licensed, it will provide an additional treatment option for this patient group. Botulinum toxin type A is a purified neurotoxin complex derived from the bacterium *Clostridium botulinum*, which produces seven neurotoxins that are structurally similar but immunologically distinct. When injected into overactive muscles, it inhibits acetylcholine release which results in inhibition of muscle overactivity. Botulinum toxin type A is currently licensed in the EU for blepharospasm, hemifacial spasm and idiopathic cervical dystonia, severe hyperhidrosis of the axillae, chronic migraine, bladder dysfunctions, focal spasticity, and temporary improvement in glabellar lines.

Approximately 110,000 people will have a stroke each year in England and spasticity arises in around 30% of stroke survivors. Spasticity has a disabling effect through pain and reduced mobility, affecting quality of life and daily functioning. The physical limitations may also limit the potential success of rehabilitation and also increase the risk of falls and consequent fractures.

Treatment aims to improve function and well-being and includes antispastic oral medications (baclofen, tizanidine, dantrolene and benzodiazepines), physiotherapy, and off-label use of botulinum toxin type A. Botulinum toxin type A is currently in phase III clinical trials comparing its effect on lower-limb spasticity and clinical global impression.
TARGET GROUP

- Lower limb spasticity: post-stroke.

TECHNOLOGY

DESCRIPTION

Botulinum toxin type A (Botox; AGN191622; GSK 1358820; onabotulinum toxin A) is a purified neurotoxin complex derived from the bacterium Clostridium botulinum, which produces seven neurotoxins that are structurally similar but immunologically distinct. When injected into overactive muscles, it inhibits acetylcholine release which results in inhibition of muscle overactivity. In clinical trials, botulinum toxin type A was administered via intramuscular (IM) injection at 300 units (u) on day 1, with an optional 100u, IM injection into additional lower limb muscles followed by 400u up to 3 times every 12 weeks over a 42 week period.

Botulinum toxin type A (Botox) is licensed in the EU for:

- Blepharospasm, hemifacial spasm and idiopathic cervical dystonia
- Severe hyperhidrosis of the axillae
- Chronic migraine
- Bladder dysfunctions
- Focal spasticity
- Temporary improvement in glabellar lines

Recognised common (≥10%) adverse effects include:

- Eyelid ptosis
- Dysphagia
- Muscular weakness
- Pain
- Viral and ear infection
- Urinary tract infection
- Dysuria
- Urinary retention

Botulinum toxin type A is also in phase III trials for migraine, neurogenic bladder and spasm, and in phase II trials for benign prostatic hyperplasia, motor neurone disease and premature ejaculation.

INNOVATION and/or ADVANTAGES

If licensed, botulinum toxin type A will offer an additional licensed treatment option for this patient group.

DEVELOPER

Allergan Ltd.
AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Spasticity is a common symptom following a stroke and usually occurs within the first few days or weeks, although the timing of onset can be highly variable. It results from impaired reflex function and also induces changes in rheological muscle properties like stiffness, fibrosis and atrophy. Spasticity has a disabling effect through pain and reduced mobility, and may also limit the potential success of rehabilitation. It affects quality of life and daily functioning and can result in urinary incontinence, limited sexual intimacy, difficulties with walking, sitting and standing, and general impairment of a person’s ability to undertake activities of daily living. The physical limitations also increase the risk of falls and consequent fractures.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

CLINICAL NEED and BURDEN OF DISEASE

Stroke is the third biggest cause of death in the UK and the largest single cause of severe disability. In England, approximately 110,000 people will have a stroke each year and around 30,000 of these will go on to have a further stroke. Stroke mainly affects older people, although significant numbers of people under 55 years are also affected. Spasticity arises in around 30% of stroke survivors, of whom spasticity in the hip, knee and ankle has been reported in 50%, 54% and 66% of patients respectively. Up to 89% of post-stroke patients with spasticity report total or partial inability to work as a result of their spasticity. There is a 4-fold increase in direct costs for patients with stroke with spasticity compared with patients with stroke without spasticity. In 2012-13, there were 91,216 hospital admissions due to stroke in England (ICD10 I61-I64), resulting in 167,996 finished consultant episodes and 1,765,989 bed days. The population eligible to receive botulinum toxin type A could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance
Other Guidance


CURRENT TREATMENT OPTIONS

Treatment for post-stroke spasticity aims to improve function and well-being, and is dependent on previous response to treatment, topographical involvement and potential side effects. Antispastic oral medications such as baclofen, tizanidine, dantrolene and benzodiazepines can reduce symptoms but their use is limited by many adverse effects. Other current treatment options include:

- Physiotherapy
- Off-label use of botulinum toxin type A (not licensed in the EU for this indication)

EFFICACY and SAFETY

Botulinum toxin type A is currently used for post-stroke lower limb spasticity on an off-label basis. A 2009 systematic review concluded that botulinum neurotoxins of type A reduced post-stroke upper limb spasticity but improvement in functional ability remained to be established. The review found no significant difference between the study drug and placebo in treating post-stroke lower limb spasticity.

The following table summarises trials for this particular preparation of botulinum toxin type A (Botox) for the current proposed indication. Searches of trial registries also identified ongoing phase III trials of other preparations of botulinum toxin type A for post-stroke lower limb spasticity sponsored by Merz (Xeomin) and Ipsen (Dysport).

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01575054, 191622-116, 2011-004980-63; botulinum toxin type A vs placebo; phase III.</th>
<th>NCT00460655, BTX108512; botulinum toxin type A vs placebo; phase III.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Allergan.</td>
<td>GlaxoSmithKline.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Complete.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry.</td>
<td>Publication22, trial registry23.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada, Korea and Russia.</td>
<td>Japan.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=418 (planned); aged 18-85 years; post-stroke lower limb spasticity for ≥3 months.</td>
<td>n=120; aged 20-80 years; post-stroke lower limb spasticity for ≥6 months.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to botulinum toxin type A, 300u, IM on day 1, with optional additional 100u, IM; or placebo, IM on day 1, with optional IM dose. Open label phase: botulinum toxin type A, up to 400u, IM, up to 3 times every 12 weeks.</td>
<td>Randomised to botulinum toxin type A, 300u, IM; or placebo, IM.</td>
</tr>
</tbody>
</table>
Follow-up | Active treatment 42 weeks; follow-up not reported. | Single treatment; 12 weeks follow-up.
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Primary outcome/s | MAS-B\(^a\) score of ankle plantar flexors; clinical global impression (CGI). | Area under the curve (AUC) in MAS\(^b\) ankle score.
Secondary outcome/s | Goal attainment score; MAS-B score of optional muscles; pain. | Gait pattern scale; speed of gait; CGI; safety.
Key results | - | AUC in MAS ankle score, greater decrease in botulinum toxin type A arm compared to placebo arm, mean difference, -3.428 (95% CI -5.841 to -1.016, p=0.006). For botulinum toxin type A and placebo respectively, mean change and SD at 12 weeks: MAS, -0.56±0.69, -0.40±0.58 (p=0.240); gait pattern scale, 0.55±1.26, 0.58±1.57 (p<0.775); speed of gait, -10.14±26.93, -8.53±24.71 (p=0.585); CGI, 0.81±1.30, 0.52±1.27 (p=0.166).
Adverse effects (AEs) | - | For botulinum toxin type A and placebo respectively, AEs ≥5%: myalgia, 5%, 3%; injection site pain, 5%, 2%.
Expected reporting date | Not reported. | -

ESTIMATED COST and IMPACT

COST

The cost of botulinum toxin type A for this indication is not yet known. The cost of botulinum toxin type A (Botox) for torsion dystonias and other involuntary movements is £276.40 for a 200u vial\(^{24}\).

IMPACT - SPECULATIVE

Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: improved quality of life for patients and carers; earlier return to normal activities, including employment.
- No impact identified

Impact on Health and Social Care Services

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other:
- None identified

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\(^a\) Modified Ashworth Scale-Bohannon – measures spasticity in patients with lesions of the central nervous system.
\(^b\) Modified Ashworth Scale – measures resistance during passive soft-tissue stretching.
Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Other increase in costs:
  - Other: uncertain unit cost compared to existing treatments
- Reduced drug treatment costs
- Other reduction in costs: reduced use of secondary care/specialist services; reduced social care costs.
- None identified

Other Issues

- Clinical uncertainty or other research question identified: whilst spasticity is common in stroke survivors, this may not be the most disabling feature of their condition; only a minority of patients affected by lower limb spasticity are likely to be suitable for botulinum toxin therapy, which should be seen as an adjunct to a holistic multi-disciplinary team approach
- None identified

REFERENCES

9 Lundstrom E, Smits A, Borg J et al. Four-fold increase in direct costs of stroke survivors with spasticity compared with stroke survivors without spasticity. The first year after the event. Stroke 2010;41:319-324.

Clinical expert opinion