

Botox® Abbreviated Prescribing Information

Presentation: Vial containing 100 units (U) *Clostridium botulinum* type A neurotoxin complex (900kD). **Indications:** Symptomatic relief of blepharospasm, hemifacial spasm, idiopathic cervical dystonia (spasmodic torticollis) and severe axillary hyperhidrosis. Focal spasticity - dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients (two years or older) and wrist and hand disability due to upper limb spasticity associated with stroke in adults. Safety and efficacy in the treatment of blepharospasm, hemifacial spasm, idiopathic cervical dystonia, or focal hyperhidrosis in children has not been demonstrated. **Dosage and Administration:** See Summary of Product Characteristics for full information. Reconstitute with sterile unpreserved normal saline (0.9% sodium chloride for injection). BOTOX® doses are not interchangeable with other preparations of botulinum toxin. **Blepharospasm:** Inject using a 27-30 gauge needle. Initially, 1.25-2.5 U injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Subsequently, the dose may be increased up to two-fold. Initial dose should not exceed 25 U per eye. Total dose should not exceed 100 U every 12 weeks. **Hemifacial spasm:** Treat as for unilateral blepharospasm (as above). Inject other affected facial muscles as needed. **Cervical dystonia:** Inject using a 25, 27 or 30 gauge needle (for superficial muscles) or 22 gauge (deeper musculature). Tailor dosing to individual patient based on the head and neck position, location of pain, muscle hypertrophy, body weight and response. Do not inject sternocleidomastoid muscle bilaterally. Maximum total dose usually not more than 200 U. **Hyperhidrosis of the axillae:** Inject using a 30 gauge needle. Inject 50U intradermally to each axilla, evenly distributed in multiple sites 1-2 cm apart. **Paediatric cerebral palsy:** Inject using a 23-26 gauge needle into the medial and lateral heads of the affected gastrocnemius muscle. Recommended total dose: 4 U/kg. Divide dose between two limbs if injected on same occasion. Repeat dose not more frequently than every two months. **Focal spasticity associated with stroke:** Inject using a 25, 27 or 30 gauge needle (superficial muscles) or longer needle for deeper musculature. Multiple injection sites may facilitate more uniform contact with the innervation areas of the muscle, especially in larger muscles. Tailor dose and number of sites based on size, number and location of muscles involved, the severity of spasticity, and the presence of local muscle weakness. **Contra-indications:** Known hypersensitivity to any constituent. Generalised disorders of muscle activity (e.g. myasthenia gravis). Concomitant use with aminoglycoside antibiotics or spectinomycin. Bleeding disorders of any type, anticoagulant therapy and whenever there is any reason to avoid intramuscular injections. Pregnancy or lactation. **Warnings/Precautions:** Relevant anatomy and changes due to prior surgical procedures must be understood prior to administration. Extra caution with injection sites close to structures such as the carotid artery and pleural apices. Do not exceed recommended dosages and frequencies of administration. Adrenaline and other anaphylactic measures should be available. For intramuscular injection and in the treatment of hyperhidrosis for intradermal injections ONLY. **Blepharospasm:** Reduced blinking following injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with Vllth nerve disorders. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid areas to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. **Cervical Dystonia:** Limiting dose into the sternocleidomastoid muscle to less than 100 U may decrease the risk of dysphagia. **Hyperhidrosis of the axillae:** Consider secondary causes of hyperhidrosis to avoid symptomatic treatment without the diagnosis and/or treatment of underlying disease. **Focal Spasticity associated with paediatric cerebral palsy and stroke:** Not intended as a replacement for the usual standard of care regimens. Not likely to be effective in improving range of motion at a joint affected by a fixed contracture. **Interactions:** Effect may be potentiated by aminoglycoside antibiotics or other drugs that interfere with neuromuscular transmission e.g. tubocurarine-type muscle relaxants. Polymyxins, tetracyclines, lincosamycin and muscle relaxants should be used with caution. **Adverse Effects:** Side effects may occur from misplacement and injection site burning. Less frequent: hyperaesthesia, arthralgia, asthenia, pain, burstitis, dermatitis, headache, injection site hypersensitivity, malaise, nausea, paresthesia, postural hypotension, pruritus, rash, incoordination, amnesia, circumoral paresthesia, depression, insomnia, peripheral oedema, vertigo. **Basic NHS Price:** £128.93. **Marketing Authorization Number:** 0426/0074. **Marketing Authorization Holder:** Allergan Ltd, Coronation Road, High Wycombe, Bucks HP12 3SH. **Legal Category:** POM. **Date of preparation:** February 2003. Further information is available from: Allergan, Coronation Road, High Wycombe, Bucks HP12 3SH.



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Consortium of Multiple Sclerosis Centres

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Neurologists interested in multiple sclerosis should take notice of the Consortium of Multiple Sclerosis Centres. It was set up in 1986 by a panel of neurologists who felt that the National Multiple Sclerosis Society of the US was too focused on aetiology and cure, neglecting care, in the widest sense, of people with multiple sclerosis. To begin with their work was perhaps more fluffy than most neurologists would be comfortable with. But they have recently widened their scope to evangelise good neurological practice. For instance, at this meeting they held informative sessions on standards in CSF analysis and MRI techniques. A month ago, they held a meeting on the significance of neutralising antibodies in interferon therapy, which was considered too highly charged to be held in the US and so took place in London. Here are my highlights:

- One of the sexy topics of multiple sclerosis research at present is cortical pathology. It seems we had forgotten that the grey matter contains myelinated fibres. Unpublished data from Bo and colleagues in Norway was presented to show that up to 24% of frontal cortex (10% of parietal cortex) may be demyelinated in multiple sclerosis patients.
- As usual, there was much talk at this conference about the need for early treatment of multiple sclerosis. Yet, interestingly, I was unable to find a single US neurologist who had adopted the new "McDonald criteria" for diagnosis of MS in their practice. This allows for the diagnosis of definite multiple sclerosis after one clinical event, if a scan three months later shows an active lesion.
- Epidemiological studies, the rockbed of multiple sclerosis research, are becoming more and more widespread. For instance, the first such studies in Latin American countries reported a prevalence of 1.5 / 100,000, which does not make a lot of sense when disease incidence was also recorded at 1 / 100,000. Typically, when prevalence is measured again, it goes up; witness the 2002 prevalence of 49 / 100,000 in Novosibirsk, a city in Asian Russia, compared to 29 / 100,000 in 1986. This probably reflects increased diagnostic accuracy.
- One of the curiosities of multiple sclerosis research has been that bladder symptoms seem to respond to any treatment, however wacky, such as hyperbaric oxygen. So it was no surprise, but nonetheless interesting, to read that a study of 41 patients treated with either standard medical care, acupuncture or combinations of the both all improved post micturition bladder volume and general



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measure of well-being (the SF-36). Great medicine, that placebo.

- With great fanfare, the "final results" of The EVIDENCE trial were reported. If ever there was a case of flogging the horse that had already bolted, this was it. The juice from the EVIDENCE data has already been squeezed out and we were offered the pith on a silver platter. EVIDENCE was always designed more to help lawyers than clinicians. To recap, Betaseron® was the first interferon onto the US patch. Avonex® appeared next and soon dominated the market, even acquiring hallowed "orphan drug" status with the FDA. This meant that Rebif®, which contains the same active ingredient as Avonex, was not allowed across the Atlantic from Europe, where it was doing very well. So Serono, who make Rebif, quite reasonably set up a trial (EVIDENCE) to mount a legal challenge on Avonex's orphan drug status on the grounds of efficacy. They showed that Rebif was more effective than Avonex at reducing relapses and MRI lesion formation over a 48-week period. This is not terribly surprising, as Rebif is over four times the dose of Avonex (44mcg of IFN- β 1a, given subcutaneously three times weekly, versus 30mcg given IM once weekly). Clearly an effect over 48 weeks is neither here nor there to someone in their twenties faced with multiple sclerosis. But the paper was published, the FDA was impressed and the gates for Serono to enter the US multiple sclerosis treasure trove were opened. Fair enough. But Serono maintained blinding in the trial until the last patient had completed 48 weeks treatment, which means that the average time on the trial was 64 weeks. And so they want to tell us the final "final results"....

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