

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of NeuroBloc. This scientific discussion has been updated until 1 February 2004. For information on changes after this date please refer to module 8B.

1. Introduction

NeuroBloc contains the active substance Botulinum Toxin Type B (BoNT-B). It is one of seven serologically distinct toxins produced by the bacterium *Clostridium botulinum*: the other ones are A, C, D, E, F, and G. All serotypes cause paralysis by inhibition of the release of acetylcholine and are candidates for therapeutic agents. The seven serotypes are antigenically distinct but have a common subunit structure. Each serotype light chain cleaves a specific residue of one or more of the proteins involved in the neurotransmitter release process, conferring specificity to the process of blocking neurotransmitter release. As a result, patients who develop neutralising antibodies to one serotype should retain responsiveness to another serotypes.

When injected directly into a muscle NeuroBloc causes a localised paralysis that gradually reverses over time.

Dystonia is a syndrome of sustained muscle contraction frequently causing twisting and repetitive movements or abnormal postures. The abnormal movements resulting from dystonia are diverse, with a wide range in speed, amplitude, repetitiveness, torsion, forcefulness, distribution in the body, and relationship to rest or voluntary activity. Focal dystonias are those where only a specific region of the body is affected. When this region is the neck it is called cervical dystonia (CD) or spasmodic torticollis.

Any dystonia may be a severe and incapacitating disease and cervical dystonia is no exception. In many cases it produces a level of disability that precludes a normal lifestyle. The suffering is not only determined by the abnormal postures and abnormal muscular contractions but also, in many cases, by pain.

There are very few studies of prevalence and incidence of focal dystonias. In Europe the estimated prevalence of focal dystonias (all types including cervical dystonia) is 116.9 per million. Cervical dystonia alone has a prevalence that varies with age strata but on average is 67 per million. Botulinum Toxin Type A (BoNT-A) is the first line option for treatment of CD. A small (5-10%) proportion of patients have primary resistance to the effect of BoNT-A. In addition, there is another fraction of patients (estimates are variable but reach 20%) that become resistant to BoNT-A after several courses of treatment. In these the most likely cause for such resistance, but not the only one, is the development of neutralising antibodies to BoNT-A.

NeuroBloc is indicated for the treatment of cervical dystonia, (torticollis).

2. Chemical, pharmaceutical and biological aspects

Composition

NeuroBloc is a sterile solution of Botulinum Toxin Type B formulated at 5000 U/ml in a pH 5.6 buffer containing disodium succinate, sodium chloride, human serum albumin, sodium caprylate, sodium acetyltryptophanate, hydrochloric acid and water for injections. It is available in three presentations: 2500 U in 0.5 ml, 5000 U in 1.0 ml and 10,000 U in 2.0 ml, all filled in 3.5 ml vials.

The units of potency are mouse lethality units, and are specific to NeuroBloc (not related to units of other botulinum toxin products).

The primary container consists of a 3.5 ml Type I (Ph.Eur.) colourless glass vial closed with grey butyl rubber, siliconised stoppers and aluminium overseals.

Phase I and II clinical studies were performed with material having the same composition of excipients and concentrations of the active substance ranging from 26 to 5000 U/ml. The Phase III programme was conducted with material having an identical composition to the proposed commercial formulation. Comparability studies have been performed demonstrating equivalence of products from the site for the manufacture of the clinical trial lots and the site for the manufacture of the commercial material for the EU market.

During the development of the product, the level of excipients was selected to provide stability during storage, minimise non-specific protein adsorption and maintain osmolarity.

Active substance

NeuroBloc is a formulation of Botulinum Toxin Type B neurotoxin and is expressed as a protein complex by the spore-forming anaerobic bacterium *Clostridium botulinum*, during fermentation. This strain is a wild-type non-recombinant organism. The toxin is synthesised by the bacterium as a single chain polypeptide of approx. 150 kDa that is activated during the fermentation process via a proteolytic cleavage (nicking) by endogenous proteases. The nicked protein is a fully active double-chain polypeptide consisting of a heavy chain (100 kDa) and light chain (50 kDa) connected by a disulphide bond. The toxin is present in its native form as a complex of toxin and non-toxin proteins with a molecular weight of approx. 700 kDa.

Fermentation

The active neurotoxin is produced by bacterial fermentation of *C.botulinum*. A two-tier cell bank system is used with a master cell bank (MCB) and a working cell bank (WCB). The MCB was used to produce the WCB. Characterisation of the MCB is limited to the identification as *C.botulinum* by biochemical profiling and gram-staining. Extensive characterisation of the WCB by testing for culture purity, cell morphology and identity is conducted for each batch. The history and initial source of the MCB have been satisfactorily addressed.

The manufacturing process is controlled with a series of in-process tests designed to ensure cultural purity, morphology and quality. In-process specifications have defined acceptance criteria. Assurance is given that raw materials of animal origin used during the fermentation process do not present a risk of BSE/TSE.

Purification

The downstream processing of the active substance is a sequence of validated chromatographic steps. In-process controls and specifications are adequate to control the quality and consistency of production. Maximum lifetimes for the columns and other process systems have been set.

Characterisation

The active substance has been characterised using a combination of traditional and state of the art physicochemical techniques.

The active substance is adequately controlled by a combination of physicochemical, biological and immunological methods. Appropriate specification has been set. All analytical procedures have been validated. Batch analysis data for four-process performance qualification batches and three consecutive conformance batches have been provided and demonstrate a consistent production of the active substance.

Other Ingredients

All excipients (except sodium succinate) meet the requirements of Ph.Eur. For sodium succinate, (for which there is no Ph.Eur. monograph), in house specifications and test methods have been set. A plasma master file and details of the virological testing performed on the HSA were provided.

All packaging materials comply with the requirements of Ph.Eur.

Product development and finished product

The manufacturing of NeuroBloc comprises:

- Manufacture of active and intermediate product at Elan Pharmaceuticals, (NPF), South San-Francisco, California, USA.
- Manufacture of final dosage form by Gensia Sicor Pharmaceuticals, Irvine, California, and USA.
- Packaging and labelling of the product at Galen Ltd., Northern Ireland, UK (primary assembly site and site for EU testing and release) or at Gensia Sicor Pharmaceuticals, Irvine, California, US (secondary site).

Manufacturing and shipping processes have been validated for the above sites and are considered satisfactory.

The finished product is adequately controlled by a combination of physico-chemical, biological and immunological methods. Appropriate specifications have been set. All methods used for routine control have been described and validated.

Stability of finished product

The stability results show a good stability profile for the finished product when stored at 2-8°C for up to 18 months. The company commits that the HSA remains within its shelf life throughout the shelf life of the finished product.

3. Toxicopharmacological aspects

Pharmacodynamics

The mode of action of botulinum toxins is the inhibition of acetylcholine release at the neuromuscular junction. As a consequence a localised paralysis occurs which subsequently recovers through a mechanism which is not absolutely clarified and seems to involve the regeneration of motor nerve endings and re-establishment of a functional connection with the motor end plate on the muscle. No formal studies were conducted to study the mechanism of recovery of muscular strength or the time of muscle/nerve terminal recovery following NeuroBloc treatment. For the methods of action and the mechanism of recovery, reference is made to published studies.

The paralytic activity of NeuroBloc was assessed *in vivo* in mice and monkey models, and was expressed by the magnitude of the reduction of the M-wave amplitude of the evoked compound muscle action potential (CMAP) for several muscles after the intramuscular injection of NeuroBloc. NeuroBloc induced a significant dose-dependent reduction of the evoked compound motor response for all muscles tested by 2 weeks after injection. Recovery was observed after 8-16 weeks depending upon dose.

A comparison of the relative paralytic potencies of Botulinum Toxin Type A (Botox®) and NeuroBloc was conducted in cynomolgus monkeys. For both toxins, the doses used induced dose-dependent decreases of M-wave amplitude for all muscles. The maximum depression was observed at one month post-dose. Paralysis was not reached. Paralytic doses (80% depression of M-wave) were calculated from the dose-response curve. It was concluded that a higher dose of NeuroBloc than of Botulinum Toxin Type A was required to cause an equivalent degree of paralysis.

No signs of systemic neurotoxicity or modifications of the M-wave amplitude of the contralateral muscles were observed in these studies.

Pharmacokinetics

Pharmacokinetic characterisation of NeuroBloc was not performed. The justification for this was based on the difficulties related to the assay/detection of the very small doses, which are to be injected, coupled to the possibility that the protein would be cleaved by tissue proteases before reaching the circulation.

Toxicity

All pivotal toxicity studies were conducted according to GLP requirements.

Single Dose Toxicity

Studies were conducted using the i.m. route of administration in cynomolgus monkeys.

Animals treated with up to 1440 U/kg appeared normal and healthy following injection. Body weight and food consumption of these animals were not changed during the study period (14 days). Doses of 1440 U/kg up to 2400 U/kg caused signs and symptoms of systemic botulism but animals showed an improvement by the end of the study (14-15 days) and therefore these doses were not life threatening. The dose of 2400 U/kg was found to be lethal.

Repeat Dose Toxicity

The therapeutic and toxic effects of single and repeated doses of NeuroBloc were evaluated in cynomolgus monkeys. Animals were assigned to either an efficacy phase (doses of 12, 24 or 48 U/kg) or a toxicity phase (doses of 120 or 240 U/kg). The total dose was divided over 5 muscles. Four weeks after injection, animals receiving an initial dose of either 24 U/kg or 120 U/kg received additional doses of 48 U/kg and 480 U/kg respectively. Contralateral muscles were not injected.

Electrophysiologic measures of central nervous system neurotoxicity or in the sural sensory velocity/amplitude did not reveal any changes and systemic muscle toxicity (expressed by reduction of M-wave of the contralateral muscles) was not observed in any of the groups, even upon re-injection of total doses of 480 U/kg.

A decrease of the muscle tone was observed at all dose levels and high dose animals progressed to inability to grasp. Paralysis interfering with normal activities like sitting, standing, jumping or eating was not observed in any animal. Food consumption was considered good, but sporadically moderate or poor in every group. Body weight and ophthalmoscopic examinations as well as clinical chemistry parameters did not reveal systematic drug-related changes.

Reproductive toxicity

Reproduction toxicity studies were not conducted because the high molecular weight of NeuroBloc makes it unlikely to cross the placental or testicular barriers. Accordingly, NeuroBloc administration is not to be recommended during pregnancy and lactation.

Genotoxicity

The mutagenic potential of NeuroBloc has not been evaluated. Given the localised administration of the product and lack of systemic exposure, the risk of genotoxic effects is considered to be minimal.

Carcinogenicity

Carcinogenicity studies were not conducted which is acceptable based on the low frequency of administration of NeuroBloc.

Local tolerance

Local tolerance was not evaluated in a formal study. However, there was no evidence of tissue reactivity at the injection site in any of the pharmacology or toxicology studies performed.

Immunogenicity

Blood samples for possible subsequent antibody titration were collected in the repeat dose studies in monkeys. These samples have not been analysed. The company states that the collection and evaluation of antibody data from patients treated with NeuroBloc is ongoing. It is accepted that the non-clinical data are superseded by these clinical results.

Special Toxicity studies

Comparability studies

An *in vivo* comparability programme was conducted to compare the pharmacological properties of NeuroBloc manufactured at two different facilities. Studies comparing paralytic activity and diffusion properties were performed in mouse and monkey models. The results of these studies suggested that the preparations were bioequivalent with respect to their paralytic potency and diffusion properties.

4. Clinical aspects

Table A : Pharmacokinetic studies

Number / Title	No. volunteers/patients	Dose and regimen	Pharmacokinetic parameters
AN072-120: Electrophysiologic Response of the Extensor Digitorum Brevis to varying doses of intramuscularly injected BotB in normal subjects	18 healthy volunteers	1.25, 2.5, 5, 7.5, 10, 15, 20, 25, 30, 40, 80, 120, 160, 240, 320, 400, 480 U. 2 different doses injected into each EDB muscle of each subject	M-wave amplitude, area and mean rectified voltage (MRV) following stimulation of peroneal nerve.
AN072-121: Electrophysiologic Response of the Extensor Digitorum Brevis to varying doses of intramuscularly injected BotB (Botulinum Toxin type B) and Botox in normal subjects	11 healthy volunteers	NeuroBloc: 20-480 U Botox: 1.25U-10 U NeuroBloc injection into one EDB and Botox injected in the contra-lateral EDB for each subject	M-wave amplitude, area and MRV following stimulation of peroneal nerve.

Table B : Safety, tolerability, Dose ranging studies

Number / Title	Study design	No. patients Dose and regimen	Inclusion criteria	Endpoints
ANO72-001: A dose ranging safety evaluation of Botulinum toxin serotype-B in patients with Cervical Dystonia (Torticollis)	OL	8; up to 5 injections, 100-1200U into defined neck/shoulder muscles	Cervical dystonia (CD), responder to type A toxin	Tsui torticollis scale scores and pain scores.
ANO72-002: An open label, dose-escalation safety and preliminary efficacy study of Botulinum toxin serotype B in patients with cervical dystonia (torticollis) who have become resistant to serotype A.	OL, MC	12 ; up to 4 injections, 100-1430 U into defined neck/shoulder muscles	Cervical dystonia (CD), resistant to type A toxin	TWSTRS subscales (1° endpoint: Severity), TWSTRS-total, patient analog pain assessment, patient and investigator global assessments
ANO72-003: An open label, dose-escalation safety and preliminary efficacy study of Botulinum toxin serotype B in patients with cervical dystonia (torticollis)	OL, MC	28; up to 4 injections, 300-12.000U into defined neck/shoulder muscles	Cervical dystonia (CD), responder to type A toxin	TWSTRS subscales (1° endpoint: Severity), TWSTRS-total, patient analog pain assessment, patient and investigator global assessments

Table C : Placebo controlled studies.

Number / Title	Study design	No. patients Dose / regimen	Inclusion criteria	Endpoints
ANO72-008: A double-blind, single dose, dose-finding, safety tolerability and preliminary efficacy study of BotB (Botulinum toxin type B) in patients with idiopathic cervical dystonia (C.D.)	R, DB, PC, MC	85; single injection placebo, 400U, 1200U, 2400U into defined neck/shoulder muscles	Cervical dystonia. Up to 50% toxin type A resistant patients	1° endpoint: clinical benefit (≥ 3 pts and $\geq 20\%$ improvement in TWSTRS-Severity) Baseline to week 4, 1200U vs. placebo.
ANO72-009: A double-blind, placebo-controlled, single-treatment, dose-finding, safety, tolerability and preliminary efficacy study of BotB (Botulinum toxin type B) at various doses in patients with ideopathic C.D.	R, DB, PC, MC	122; single injection placebo, 2500U, 5000U, 10.000U into defined neck/shoulder muscles	Cervical dystonia. Up to 50% toxin type A resistant patients	1° endpoint: pairwise comparison active to placebo. TWSTRS-total baseline to 4 weeks. Clinical benefit $\geq 20\%$ improvement in TWSTRS scores, baseline to week 4.
ANO72-301: A double-blind, placebo-controlled, single dose, safety and efficacy study o BotB (Botulinim toxin type B) in patients with C.D.	R, DB, PC, MC	108; single injection placebo, 5000U, 10.000U in defined neck/shoulder muscles	Cervical dystonia Patients responsive to toxin type A	1° endpoint: TWSTRS-total score baseline to week4. Primary contrast 10.000U vs. placebo. Supportive: Patients Global assessment at week 4.
ANO72-302: A double-blind, placebo-controlled, single dose, safety and efficacy study o BotB (Botulinim toxin type B) in type A resistant patients with C.D.	R, DB, PC, MC	77; single injection placebo, 10.000U in defined neck/shoulder muscles	Cervical dystonia Patients resistant to toxin type A	1° endpoint: TWSTRS-total score baseline to week4. Supportive: Patients Global assessment at week 4.

Table D : Ongoing studies (at the time of submission of the Marketing Authorisation Application)

Number / Title	Study design	No. patients Dose, route of administration and regimen	Inclusion criteria	Endpoints
AN072-351: An open-label, safety study of NeuroBloc (Botulinum toxin type B) in patients with C.D.	OL, MC	260; repeat injections more 12 weeks apart, 5000-10.000 U initially, up to 15.000U if appropriate ; In defined neck/ shoulder muscles	Cervical dystonia Patients who participated in previous NeuroBloc studies or screening failure for study ANO72- 302, or txoin-naïve and post-surgical/phenol injected patients	TWSTRS-total score and subscales. Patients Analog Pain and Global assessment at week 4 after each injection.

Number / Title	Study design	No. patients Dose, route of administration and regimen	Inclusion criteria	Endpoints
ANO72-352: An open-label, dose escalation, safety and tolerability study of Botulinum toxin type B in patients with C.D.	OL, MC	138; up to 3 injections, upon return to baseline; 10.000U, 12.500U and 15.000U; In defined neck/shoulder muscles	Cervical dystonia Type A responsive or resistant (< 50%)	TWSTRS- subscales and total. Patients Analog Pain and Global assessment at week 4 after each injection.

DB : double blinded
R : randomised
PC : placebo controlled

OL : open label
MC : multi centre

Clinical Pharmacology

Mechanism of action

Botulinum type B neurotoxin reversibly paralyses or weakens skeletal muscles by inhibition of acetylcholine release from synaptic vesicles in the terminals of cholinergic motor nerves.

Pharmacodynamics

Two pharmacodynamic studies were carried out in 28 healthy volunteers to demonstrate Botulinum Toxin Type B biological activity in man (table A). The muscle used as the model was the extensor digitorum brevis (EDB) of the lower limb. In the EDB paradigm the level of paralysis was assessed by measuring electrophysiologic parameters, namely the M-wave parameters [amplitude, area and mean rectified voltage (MRV)]. The degree of reduction of the M-wave was related to the dose of NeuroBloc administered.

Study ANO72-120

This study was conducted to assess the EDB model itself and the dose range needed to generate a dose-response curve for NeuroBloc in normal volunteers. 17 different NeuroBloc doses were tested. The rate of fall in the M-wave amplitude area and MRV was similar in all subjects in this study, becoming maximal by approximately day 6, post-injection. The maximal effect achieved at the 480U dose level was approximately 25% of the pre-injection value. This dose-response curve demonstrated with NeuroBloc is similar to that demonstrated previously with one of the commercial formulations of BoNT-A (Botox).

Safety data: no patients developed resistance to NeuroBloc. The adverse events (AEs) attributable to the product consisted of pain (three subjects), hypesthesia (one subject), and myasthenia (one subject). These events were mild in all subjects, and none lasted more than four days. There were no reported deaths or serious AEs.

Study ANO72-121

The objective of this study was to compare the effect of various doses of NeuroBloc and Botox on electrophysiological measures in normal subjects.

The following doses were tested (each dose level were studied in two EDB): Botulinum Toxin Type A (BoNT-A, Botox®: 1.25U, 2.5U, 5U, 7.5U, 10U); NeuroBloc (20U, 80U, 160U, 320U, 480U). The measurements were done in days 2, 4, 6, 9, 11, 13 and 14 after injection.

The rate of fall in the M-wave amplitude and area was similar in Botox treated muscles compared with NeuroBloc treated muscles with maximal effect being present by approximately day 6 post-injection.

Intramuscular injection with BoNT of either the A subtype or the B subtype produces a dose dependent fall in M-wave amplitude and area. These curves both approximate logarithmic curves with incrementally less effect at higher doses as the maximal effect is approached.

Adverse events in Study AN072-121 were minimal and of short duration, lasting from a few hours to one week. There were no deaths and no serious AEs. Three out of the 10 volunteers reported foot pain that was considered to be related to study drug.

Pharmacokinetics

Pharmacokinetic studies were not conducted; as such studies would require the administration of doses of toxin that would produce the death or severe sequelae of the subjects. At tolerable doses the concentration of botulinum toxin in the systemic circulation after intramuscular injections are in the order of fentograms. There is no assay available that is sensitive enough to measure those quantities.

Interaction studies

No formal drug interaction studies were performed because it is not expected that systemic interactions will occur given the route of administration, the local effects of Botulinum Toxin Type B and the known class of the drug. Published clinical safety and pharmacovigilance data for both formulations of type-A toxin indicate that, apart from the expected additive effects of drugs which cause muscle paralysis and muscle weakness (e.g. curare-like medicines), no significant hazards or interactions are known or anticipated. Caution should be exercised in patients receiving aminoglycosides.

Clinical Efficacy

Dose-response studies (table B)

Studies ANO72-001, ANO72-002 and ANO72-003 were preliminary open-label safety and tolerability studies carried out to assess the safety range of the drug to support further clinical trials. A total of 48 patients with cervical dystonia (CD) were enrolled in these studies and received doses of between 100 U and 12,000 U. The data demonstrate that individual doses of up to 12,000 U and cumulative doses up to 12,000 U were well tolerated. The efficacy data suggested a positive effect at 2400 U that increased at higher doses. Development of antibodies to Botulinum Toxin Type B was not detected.

Main clinical studies (table C)

Efficacy of Botulinum Toxin Type B in the treatment of cervical dystonia (CD) was studied in two distinct populations: patients responsive to BoNT-A and patients resistant to BoNT-A.

Efficacy measurements were based on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). This is a validated scale that was specially developed to be used in clinical trials. The TWSTRS-Total is a comprehensive scale that assesses multiple components of a patient's dystonia across a spectrum of disease severity, i.e. clinical severity, disability and pain. The patient and principal investigator assessment of global changes and the patient assessment of pain were obtained using visual analogue scale (VAS).

With the exception of Study AN072-008, in which the primary endpoint was defined as the mean change in the TWSTRS-Severity score baseline to Week 4, the primary endpoint in all controlled studies was the mean change in the TWSTRS-Total score baseline to Week 4. The secondary endpoint measured were the changes from baseline in TWSTRS-Total at Week 8 and Week 12 plus the Patient Global Assessment and Principal Investigator Global Assessment, at Week 4. Tertiary endpoints included changes from baseline at each study visit in TWSTRS-Severity, TWSTRS-Disability, TWSTRS-Pain scores, and Patient Analogue Pain Assessment. Safety data were also collected at each timepoint. A responder to treatment was defined as showing a 20% improvement in TWSTRS-Total.

Efficacy in BoNT-A responsive patients

AN072-008 (Phase II)

The primary objective of this randomised double blind, placebo-controlled study was to evaluate the safety and tolerability of three doses of NeuroBloc (400 U, 1200 U and 2400 U) versus placebo in patients with cervical dystonia (CD). Secondary objectives were to provide information to aid in the selection of doses for future studies and to evaluate the use of different rating scales to measure outcomes in future pivotal trials.

The efficacy variables included TWSTRS scores (Severity, Disability, Pain, and Total), Patient Analogue Pain Assessments, Patient Global Assessments, and Investigator Global Assessments. The primary efficacy variable was the proportion of patients who showed clinical benefit from baseline to Week 4 (responders) as indicated from the TWSTRS-Severity score and comparing patients who received placebo with those who received 1200 U Botulinum Toxin Type B. Clinical benefit was defined as ≥ 3 points and 20% improvement from baseline TWSTRS-Severity score to Week 4.

A total of 85 patients entered and 30 patients (35%) met the criteria to complete the study. All but 2 patients who were withdrawn from the study were withdrawn because they met the protocol-defined criteria for 'lack of response'. The percentages of withdrawals were similar in the placebo, 400 U and 1200 U dose groups (67%, 71% and 73%, respectively), whereas only 48% were withdrawn in the 2400 U group. Of the two withdrawals not related to response, one was a placebo patient.

NeuroBloc was safe and well tolerated at single doses up to 2400 U. A single dose of 2400 U was shown to be effective using the TWSTRS-Total and Pain scores and the Patient and Investigator Global Assessment scores. Doses below 2400 U are unlikely to be effective and the data suggest that the duration of effect is dose-dependent.

AN072-009 (Phase II)

The primary objective of this randomised double-blind placebo-controlled study was to evaluate the safety and tolerability of three doses of NeuroBloc (2500 U, 5000 U, 10,000 U) versus placebo in patients with CD by assessing clinical safety parameters, laboratory tests, and adverse events. Additional objectives were to assess the suitability and validity of the use of various efficacy parameters (TWSTRS scores, Sickness Impact Profile, Analogue Pain Assessment, Investigator Global Assessment, and Patient Global Assessment) as outcome measures for future pivotal trials.

A total of 122 patients entered the study and all completed the protocol. No patient withdrew from the study because of an adverse event (AE). Twenty one percent of BoNT-A resistant patients were included in this study.

Patients with a 20% baseline to Week 4 improvement in TWSTRS-Total score were considered "responders" and returned to the clinic every four weeks for up to a maximum of four months. The primary efficacy analysis compared the TWSTRS-Total scores from baseline to Week 4 between treatment groups by analysis of covariance (ANCOVA). Secondary analyses of the TWSTRS-Severity, -Disability, and -Pain subscales were also performed by ANCOVA.

All treatment groups showed improvement in TWSTRS scores from baseline to Week 4. All of the TWSTRS scores tended to improve as the dose of NeuroBloc increased (see below). In the analysis of covariance on baseline to Week 4 TWSTRS-Total scores for intent-to-treat patients, the overall difference among treatment groups was highly statistically significant ($p = 0.0001$). In addition, the analysis of dose-response was significant (Total, $p = 0.0001$; Severity, $p = 0.0009$; Disability, $p = 0.0004$; Pain, $p = 0.0004$).

Study AN072-009: TWSTRS Improvements at Week 4

	TWSTRS							
	Total		Severity		Disability		Pain	
	Score	p-value ^a	Score	p-value ^a	Score	p-value ^a	Score	p-value ^a
Placebo	3.3		1.6		0.7		1.0	
2500 U	11.6	0.0016	3.5	0.0511	3.8	0.0165	4.4	0.0019
5000 U	12.5	0.0005	4.5	0.00211	3.6	0.0122	4.3	0.0013
10,000 U	16.4	0.001	4.7	0.0007	5.4	0.0001	6.4	0.0001

a: p-value for the analysis of covariance on the baseline to Week 4 data; comparison of treatment groups with placebo group

Mean analogue pain ratings and Patient and Investigator Global assessments also improved in the NeuroBloc-treated groups.

The study showed that NeuroBloc was safe, well tolerated and effective at single doses of 2500 U, 5000 U, and 10,000 U and that there is a dose-response for clinical benefit and typical adverse events, (like dysphagia). The trial did not assess directly the time to onset of clinical benefit nor the duration of effect. Estimates of time to onset of clinical benefit and duration of effect were obtained by indirect methods. Duration of effect (obtained from the time for which patients continued in the study) showed a trend towards being dose-dependent.

AN072-301 (Phase III)

The objectives of this study were to evaluate the safety and efficacy of two doses of NeuroBloc (5000 U and 10,000 U) versus placebo in patients with CD who were known to be responsive to Botulinum Toxin Type A.

A total of 109 patients were enrolled, 36 in the placebo group, 36 in the 5000 U group, and 37 in the 10,000 U group. Two patients in the placebo group, one patient in the 5000 U group and one patient in the 10,000 U group withdrew from the study.

The primary efficacy variable was the change in TWSTRS-Total score from baseline to Week 4 and the primary contrast performed on this variable was a test that compared of the 10,000 U and placebo treatment groups using analysis of covariance. The supportive secondary variable was the Patient Global Assessments at Week 4. Additional secondary variables were the Principal Investigator Global Assessments at Week 4 and the TWSTRS-Total scores at Weeks 8 and 12 (see below).

Study AN072-301

Variable	Mean result		p-value ^a
	Placebo (n=36)	10,000 U (n=37)	
Primary			
Improvement in TWSTRS-total at Week 4 ^b	4.3	11.7	0.0004
Secondary			
Patient Global Ass. at Week 4 ^{c,d}	43.6	64.6	0.0001
Principal Investigator Global Ass. at Week 4 ^d	52.0	64.2	0.0038
Improvement in TWSTRS-total at Week 8 ^b	2.3	8.4	0.0032
Improvement in TWSTRS-total at Week 12 ^b	1.4	4.1	NS ^e

^a comparison of the 10,000 U and placebo groups (the primary contrast). Baseline was included in the model as a covariant for the TWSTRS-total analyses.

^b mean improvement from baseline

^c prospectively defined supportive secondary efficacy variable.

^d mean value at Week 4.

^e NS= not significant

The 5000 U and placebo groups were also significantly different for the TWSTRS-Total scores from baseline to Week 4, Patient Global Assessments at Week 4, Principal Investigator Global Assessments at Week 4 and TWSTRS-Total scores at Week 8. However, the mean change noted for the 10,000 U groups was consistently greater than that for the 5000 U group.

Patients in the treatment groups experienced similar numbers and types of adverse events overall. The percentage of events that was considered related to study medication was higher in the NeuroBloc 10,000 U group than in the placebo or 5000 U groups. Patients who received NeuroBloc than by patients who received placebo experienced dry mouth and dysphagia more frequently, and the frequency increased with increasing doses. Most cases of dysphagia were mild and none was serious. NeuroBloc was safe and effective at the doses studied for the management of patients with CD.

Retrospective Kaplan-Meier analyses, using time to return to baseline TWSTRS-Total score, were conducted to estimate the duration of treatment effect. The estimated median time until return to baseline for the treatment groups was: placebo - 63 days (9.0 weeks); 5000 U - 114 days (16.3 weeks); 10,000 U - 111 days (15.9 weeks).

Additional retrospective analyses estimated the duration of effect in patients considered responders as defined in protocol. In this subset of patients approximately 53% of the responders are known to have maintained their response for at least 16 weeks.

No formal analysis of time to onset of clinical benefit (latency of effect) was conducted. However the data demonstrate that by the Week 2 visit the TWSTRS-Total score had improved significantly in the NeuroBloc treated group compared to placebo. No data before Week 2 are available.

Efficacy in BoNT-A resistant patients

To be defined as A-resistant, the patient must have met all of the following criteria: 1) have had a good clinical response to previous BoNT-A treatment(s); 2) have failed to respond to the last 2 successive "adequate" treatments (i.e. adequate dose, muscle selection and toxin administration) with BoNT-A; 3) during the last treatment session, an increased dose of toxin was administered (i.e. relative to the highest dose at which the patient had previously a "good" clinical response).

The existence of neutralising antibodies anti BoNT-A was not a requirement for defining A-resistance.

Preliminary proof of Efficacy

Studies AN072-002 and AN072-009 previously described provided preliminary proof of efficacy and dose response in A-resistant patients.

AN072-302 (Phase III)

The objectives of this study were to evaluate the safety and to confirm the efficacy of NeuroBloc versus placebo in patients with cervical dystonia who were resistant to Botulinum Toxin Type A. In addition to meeting the criteria described above, to be considered Type-A resistant, patients had to have a confirmatory Frontalis Type A Test.

A total of 77 patients were enrolled: 38 in the placebo group and 39 in the NeuroBloc 10,000 U group. Seventy-six completed the study; one patient in the control group withdrew.

The primary efficacy variable was the change in TWSTRS-Total score from baseline to Week 4. The primary contrast compared the NeuroBloc and placebo treatment groups using analysis of covariance. The secondary efficacy variables were the analysis of the Patient Global Assessments at Week 4, the Principal Investigator Global Assessments at Week 4 and the TWSTRS-Total scores at Weeks 8 and 12 (see below).

Study AN072-302

Variable	Mean result		p-value ^a
	Placebo	10,000 U	
Primary			
Improvement in TWSTRS-total at Week 4 ^b	2.0	11.1	0.0001
Secondary			
Patient Global Ass. At Week 4 ^{c,d}	39.5	60.2	0.0001
Principal Investigator Global Ass at Week 4 ^d	47.9	60.6	0.0001
Improvement in TWSTRS-total at Week 8 ^b	1.7	8.8	0.0002
Improvement in TWSTRS-total at Week 12 ^b	0.8	6.0	0.0129

^a comparison of the 10,000 U and placebo groups (the primary contrast). Baseline was included in the model as a covariant for the TWSTRS-total analyses.

^b mean improvement from baseline

^c prospectively defined supportive secondary efficacy variable.

^d mean value at week 4.

Retrospective Kaplan-Meier analyses, using time to return to baseline TWSTRS-Total score, were conducted to estimate the duration of treatment effect. The estimated median time until return to baseline in the treatment groups was: placebo- 59 days (8.4 weeks), 10,000 U -112 days (16 weeks). Additional retrospective analysis estimates that in patients considered responders as defined in protocol approximately 94% and 70% of patients maintained their response for at least 12 and 14 weeks, respectively. No formal analysis of time to onset of clinical benefit (latency of effect) was conducted. However the data demonstrate that there was a significant response by the Week 2 visit. No data before Week 2 are available.

Supportive studies (open label)

There are two on-going open label trials: (AN072-351, AN072-352) (see table D).

Study AN072-351 is an open-label, repeat-dosing, safety study open to all participants in the prior trials described in this report including those who had previously failed screening. A limited number of toxin naïve patients and post surgical/phenol-treated patients are also eligible for inclusion. This is primarily a safety study is to evaluate the safety of repeated doses of NeuroBloc in patients with CD. The secondary objective is to evaluate the effectiveness of repeated doses of NeuroBloc using the TWSTRS-Total endpoint. Up to 600 patients are to be enrolled in the study.

As of the data cut off for the interim analysis (May 1999), 398 patients had participated in the first treatment session and 197 of these patients had participated in a second treatment session and 55 in a third. The first treatment is NeuroBloc 10,000 U (or their current dose if enrolling from Study AN072-352 or 5000 U if not previously treated with toxin). Subsequent treatments are given at the time their TWSTRS-Total scores returned to baseline, but no sooner than 12 weeks. The subsequent doses are adjusted by the investigator on the basis of the response (rising increments of 2500 U or 5000 U). In addition to collecting safety data following repeat dosing at and above the higher doses used in the later placebo-controlled trials, this study collects efficacy data using the same endpoints used in earlier studies.

Study AN072-352 is an open-label forced dose-escalation study in NeuroBloc naïve patients classified as either Toxin Type A responsive or Toxin Type A resistant. All patients start at an initial NeuroBloc dose of 10,000 U and are eligible to proceed to the next dose cohort when they return to baseline status. The dose cohorts are 10,000 U, 12,500 U, and 15,000 U. The objectives of the study are to evaluate the safety and tolerability of repeat dosing of NeuroBloc in patients with CD at doses of 10,000 U, 12,500 U, and 15,000 U and to assess the effect of increasing doses of NeuroBloc. As of the data cut off point for the interim analysis, 138 patients had enrolled in the study. Each patient participated in up to three dosing sessions. In addition to collecting safety data following multiple dosing at and above 10,000 U the study also collects efficacy data using the same endpoints used in earlier studies.

Clinical benefit was observed at each of the three doses using the TWSTRS-Total score. The findings for other endpoints were similar.

These data suggest that it is unlikely that the use of concomitant medications confounded the results of the open-label studies, as the distribution of drugs over dose groups is broadly equivalent.

Discussion on Clinical Efficacy

Studies AN072-008, AN072-009 were primarily designed as dose finding studies. However they do provide evidence that NeuroBloc is efficacious in the symptomatic treatment of cervical dystonia in Botulinum Toxin Type A responsive patients and that there is a dose-response relationship for this beneficial effect. A series of doses were tested and the minimum beneficial dose is 2400 U. This was further confirmed by the pivotal study ANO72-301. The beneficial effect obtained is clinically meaningful (mean change from baseline in TWSTRS-Total at 4 weeks is around 25%) and occurs in approximately 50% of treated patients. Clinical benefit occurs across all dimensions of TWSTRS and is also reflected in pain scores and global assessments. These were single dose studies and, as expected, no patients developed antibodies to NeuroBloc as measured by ELISA tests.

The results of the pivotal trial ANO72-302 in Type-A resistant patients are consistent with those observed for A-responsive patients. The magnitude of the treatment effect is similar between A-resistant and A-responsive patients but the percentage of patients responding appears to be lower in the A-resistant group. From the available data it is not possible to conclude whether the response rate is truly similar or different between A-responsive and A-resistant patients.

In order to solve the absence in any of the studies of a prospective measurement of duration of effect and latency of effect the applicant produced two retrospective analyses. The first one is a retrospective *survival analysis* where the event was "time to return to baseline". Survival analysis is indeed a robust and suitable type of analysis for this time of outcome. In this particular case, the data that allowed the analysis was obtained intermittently and thus there was need to artificially refer the occurrence of the event for a point in time between to scheduled visits. This has the effect of homogenising the results. In the end the estimated duration of effect may be considered a very rough estimate. Furthermore, the event 'time to return to baseline' may not reflect the clinical practise.. The second analysis attempts to estimate the duration of effect in the responders. This is again a crude estimate of the duration of effect because it is biased towards a greater duration. However we must concede that the two analysis agree that mean duration of effect is between 12 and 16 weeks.

In order to provide an additional estimation of duration of effect, an *aggregate analysis* of studies ANO72-301/302/009 was done, using the definition of responders. In this analysis duration of effect was counted from day 0 (visit where treatment was administered) until the last visit where an improvement of 20% on TWSTRS-total from baseline was maintained. Only responders were included. This aggregate analysis produced the following results:

Aggregate analysis of responders in studies ANO72-301/302/009

Groups	Total N	Responder N	DURATION OF EFFECT							
			4 weeks		8 weeks		12 weeks		16 weeks	
Placebo	104	20	10	50%	4	20%	2	10%	4	20%
5000 U	67	37	16	43%	8	22%	6	16%	7	19%
10000 U	106	61	23	38%	21	34%	10	16%	7	11%
5000 U + 10000 U	173	98	39	40%	29	30%	16	16%	14	14%

Bold figures are the % of "continuous" responders in each duration of effect category

The analysis shows that 30% of patients maintain an improvement of at least 20% on TWSTRS for 12 weeks or longer.

A statement is included in section 4.2 of the SPC that gives a factual account of the duration of effect, based on the combined data from the 5000 U and 10000 U groups (see table). "In clinical trials the

duration of effect was variable. In the patients who responded to treatment (those who experienced an improvement in TWSTRS greater than 20% over baseline) the following duration of effect was observed: at least 4 weeks (40% of patients), at least 8 weeks (30%), at least 12 weeks (16%), 16 weeks or longer (14%)."

It is worth noting that the dose is established at 10.000U because no other dose level was tested in A-resistant patients. It is likely that the dose of 5000U is also efficacious in this patient population but this was not studied.

Clinical Safety

Patient exposure

Twenty-eight healthy volunteers were treated with NeuroBloc in two pharmacodynamic studies. The doses used were less than 500 U and the safety results can not be expected to reveal information about the tolerability of treatment in clinical practice, where the proposed starting dose is 10,000 U. The total of 568 patients exposed to NeuroBloc in the nine clinical trials received 2438 doses of NeuroBloc.

Adverse events and serious adverse events/deaths

Safety data from patients with cervical dystonia were obtained from double-blind and open-label trials. The most frequent adverse events associated with NeuroBloc treatment are dry mouth and dysphagia. These adverse effects are to be anticipated when injecting botulinum toxin into the muscles of the neck and are known also to be associated with the use of Botulinum Toxin Type A in the treatment of CD.

Overall, the majority of patients reporting AEs reported them as mild. For the event of dry mouth (nervous system), 125 patients (24%) reported a maximum intensity of "mild", 71 patients (13%) reported a maximum intensity of "moderate", 20 patients (4%) reported a maximum intensity of "severe", and for one patient (<1%), the intensity was unknown. For dysphagia (digestive system), 102 patients (19%) reported a maximum intensity of "mild", 44 patients (8%) reported a maximum intensity of "moderate", 7 patients (1%) reported a maximum intensity of "severe", and for 2 patients (<1%), the intensity was unknown. The mean and median duration over all doses were 35 days and 18 days for dry mouth and dysphagia, respectively. No cases were reported of dysphagia that needed gastric intubation.

Analysis of the number of patients reporting AEs in the placebo controlled studies reveals a clear and consistent dose response relationship between number of patients reporting treatment emergent signs and symptoms in the nervous system and a clear trend in the digestive system. Dry mouth and dysphagia are the most frequently reported AEs and are those with the clearest dose response relationship.

Data from open-label and follow-on studies demonstrate that the body systems most commonly associated with AEs are the nervous system, body as a whole, and the digestive system. There is evidence of a relationship between dose and reporting of AEs in these body systems.

Specific analyses were carried out to determine if, as might be expected, there was a relationship between the dose of NeuroBloc injected into the sterno-cleido-mastoid muscle (SCM) and the incidence and severity of dysphagia. Data from Studies AN072-301 and -302 were analysed using a logistic regression model to determine the interaction between dose injected into the SCM and the severity or frequency of dysphagia. Of the 186 patients enrolled into the two pivotal studies, 26 patients (14%) reported dysphagia. Although there was an anticipated, significant association between SCM injection and the occurrence of dysphagia ($p = 0.0001$), there was not an association between the amount of drug injected into the SCM and the severity of dysphagia. For the four controlled studies, 36 patients (10%) reported a maximum intensity of "mild," 9 patients (2%) reported a maximum intensity of "moderate," and no patients reported "severe" for dysphagia. The

information that dysphagia depends on the total dose and in particular of the dose injected in the SCM is included in the SPC.

In the two pivotal studies, 33 patients (18%) reported dry mouth. For the four controlled studies, 29 patients (8%) reported a maximum intensity of “mild,” 16 patients (4%) reported a maximum intensity of “moderate,” and four patients (1%) reported a maximum intensity of “severe” for their dry mouth.

Data from clinical trials indicate that there is a relationship between the dose of NeuroBloc injected into the sternocleidomastoid muscle and the incidence and severity of dysphagia.

Safety-related withdrawals

There were 14 withdrawals due to adverse events. It should be noted that of the 14 withdrawals only 6 were due to an AE that was considered to be related to the study drug. Two of these six patients were being treated with placebo.

Serious adverse events and deaths

During the clinical trials programme four patients died. None of the deaths was thought to be related to treatment with NeuroBloc (two cancers, a post-surgical complication following a myocardial infarction, and a sub-arachnoid haemorrhage).

Twenty-nine patients reported a total of 35 serious adverse events during treatment with NeuroBloc. Cases of cardiovascular events were reported, but do not raise any particular concern. None of the serious adverse events was considered by the investigator to be treatment-related and the majority of serious adverse events resolved.

Immunogenicity

Immunogenicity was investigated by carrying out ELISA and Mouse Neutralising Antibody Assays (MNAA) to detect the presence of antibodies directed against NeuroBloc in all patients enrolled in Studies AN072-301 and AN072-302. Samples were taken at baseline, four weeks after treatment and at the end of the study. The ELISA test is very sensitive and is capable of detecting circulating antibodies against NeuroBloc at very low titres but it is not capable of demonstrating if they are neutralising antibodies or not. The MNAA is an in vitro assay which determines if the antibodies neutralise the effects of the toxin. As of the data cut off point for filing only one case of a positive MNAA in which a clinical history consistent with secondary non-response had been observed.

Further immunogenicity data were generated from 459 patients in the ongoing extension studies AN072-351 and AN072-352: 6% of patients developed a positive MNAA, although the majority of patients continued to receive NeuroBloc treatment. The limited data available suggest that there is little difference in likelihood of an immunogenic response in A-resistant compared with A-responsive patients however insufficient data are available to draw firm conclusions. There is no evidence that NeuroBloc is more or less immunogenic than BoNT-A.

Discussion on Clinical Safety

Botulinum toxins are injected locally in the muscles judged to be involved in the abnormal posture or movement of the neck. Systemic effects or effects at distance from the locale of the injection are not expected, except for a flu like syndrome with asthenia that is described as being associated to BoNT-A treatments; this is interpreted as an unspecific immunological reaction. At a local level it is expected that in some cases the diffusion of toxin will affect some muscles that were not injected producing adverse events such as dysphagia or floppy neck. It is also expected that the anticholinergic effect of botulinum toxins may manifest in the vicinity of the local injection (dry mouth) and sometimes in more distant sites in the form of blurred vision.

The safety data obtained in relation to NeuroBloc are absolutely in accordance with what was expected. There are no significant systemic effects. The local effects of dry mouth and dysphagia are

in most cases mild to moderate and dose-dependent. The dose injected in the sternocleidomastoid muscle is predictive of the occurrence of dysphagia.

Deaths and serious adverse events were considered unrelated to treatment with NeuroBloc. Withdrawals due to adverse events are also totally acceptable and do not deserve further comment. The position of the company regarding special populations (contraindication in children and no special precautions in elderly) is adequate. Elderly were represented in trials and the parameter that should determine the treatment is the muscular bulk and not age by itself.

The company has performed a comprehensive programme to identify antibodies against NeuroBloc in the population enrolled in the controlled trials. All were screened with ELISA tests at several points in time and the positive ELISA were further studied in the Mouse neutralising antibodies assay (MNAA). The ELISA test is highly sensitive but has a low specificity. Thus there were a number of positive ELISA tests evenly distributed by placebo and active treated patients. None of these prove to be positive in MNAA. In the patients enrolled in the on-going, open-label trials all patients were tested by ELISA and MNAA. Approximately 6 % of patients developed a positive MNAA, but the data suggest that relatively few patients became unresponsive to NeuroBloc and that NeuroBloc probably has similar immunogenicity potential as Botulinum Toxin Type A. Given the limited long-term follow-up data, immunogenicity of NeuroBloc will continue to be evaluated in the ongoing studies and in the post marketing setting.

5. Overall conclusions and benefit/risk assessment

Quality

A comprehensive pharmaceutical dossier supported the application and there were no major issues identified on the quality part of the dossier. A number of points for clarification were raised. Adequate responses to these points were provided as answers to the list of questions and appropriate pharmaceutical commitments have been agreed.

Preclinical pharmacology and toxicology

The preclinical file supporting the marketing authorisation for NeuroBloc is limited. The pharmacological characterisation was mainly based on published information from the literature. The study of the toxicological profile of NeuroBloc was also very limited and the toxicity of repeated doses has not been fully explored in animal studies. However the evidence from the completed preclinical studies together with the clinical data suggest that the effect of NeuroBloc is relatively short and should be regarded as multiple single dose treatments.

The immunogenic potential, which is a relevant issue for this type of compound has not been studied, but the company has performed a comprehensive programme to identify antibodies against NeuroBloc in patients treated in the clinical trials.

In summary the limited preclinical information provided suggests that the human use of NeuroBloc, unless superceded by clinical information and experience may only be justifiable for single-dose administration in situations without a therapeutic alternative.

Efficacy

The clinical studies documented provide evidence that NeuroBloc is efficacious in the symptomatic treatment of cervical dystonia in patients responsive and resistant to BoNT-A.

Data from clinical trials suggest that efficacy is dose dependent but these trials, because they were not powered for a comparison, do not show a significant difference between 5000 U and 10,000 U. The SmPC therefore suggests that an initial dose of 5000 U may also be considered, but that a dose of 10,000 U may increase the likelihood of clinical benefit.

In order to solve the absence in any of the studies of a prospective measurement of duration of effect and latency of effect the applicant provided retrospective analyses indicating a medium time to return to baseline of 12-16 weeks. The duration of effect was variable, however in the patients who responded to treatment at Week 4 60% were still responders at Week 8, 30% were still responders at Week 12 and 14% were still responders at Week 16.

The latency for clinical effect is unknown but considered reasonable since significant efficacy was seen at 2 weeks post-injection.

Safety

NeuroBloc is injected locally in the muscles judged to be involved in the abnormal posture or movement of the neck. Systemic effects or effects at a distance from the site of injection are not expected. At a local level it is expected that in some cases the diffusion of toxin will affect some muscles that were not injected producing adverse events like dysphagia or floppy neck. It is also expected that the anticholinergic effect of BoNT may manifest in the vicinity of the local injection (dry mouth) and sometimes in more distant sites in the form of blurred vision. The dose injected in the sternocleidomastoid muscle is predictive of the presence of dysphagia.

Regarding the immunogenicity of NeuroBloc, of the patients enrolled in the controlled and on-going, open-label trials approximately 6% of patients developed a positive MNAA, but the data suggest that relatively few patients became unresponsive to NeuroBloc and that NeuroBloc probably has similar immunogenicity potential as BoNT-A. The company committed to do a further follow-up study in Europe to determine the incidence of resistance to treatment and development of neutralising antibodies to NeuroBloc in CD patients treated in multiple occasions. The study will include at least 50 % A-resistant patients.

Benefit/Risk Assessment

The documentation submitted is adequate to evaluate the quality of the medicinal product.

The preclinical file supporting the marketing authorisation application for NeuroBloc is limited, but could be accepted on the basis of the clinical experience.

The clinical studies provide evidence that NeuroBloc is efficacious in the symptomatic treatment of cervical dystonia in patients responsive or resistant to Botulinum Toxin Type A. The studies were not designed for comparison between NeuroBloc and Botulinum Toxin Type A, nor were they designed to study prospectively the duration of effect or latency of onset of effect.

The safety profile of NeuroBloc is adequate. The local effects of dry mouth and dysphagia are in most cases mild to moderate and dose-dependent. However the immunogenicity characteristics are not yet known because there is not a long enough follow-up. The Applicant has committed to continue to evaluate the immunogenicity of NeuroBloc in the ongoing studies and the post marketing setting.

The CPMP discussed the following points of concern:

- The analysis of the duration of effect
- The comparative safety and efficacy of NeuroBloc with Botulinum Toxin Type A
- Post approval comparative study of NeuroBloc against Botulinum Toxin Type A in patients with cervical dystonia.

The Applicant showed that for both Botulinum Toxin Type A and Type B the duration of effect is variable and dose related, but that most patients can be successfully managed by injections every 12 weeks. From analysis of the published trials with Botulinum Toxin Type A, there were no major differences between Botulinum Toxin Type A and B in terms of efficacy and safety at their respective recommended starting doses. There is also no evidence to suggest that patients who developed resistance to Botulinum Toxin Type A are more likely to develop antibodies to NeuroBloc.

The applicant discussed the practical problem to conduct a comparative trial between Botulinum type A and type B to establish the efficacy and duration of effect. The CPMP during their September 2000 meeting requested the company to provide them prior to opinion with a protocol synopsis of such a study. The applicant prior to the October CPMP meeting has submitted the protocol for such a post marketing study. This study will be a randomised, double blind study comparing the efficacy and safety of NeuroBloc (Botulinum toxin type B) with Botulinum toxin type A (Botox) in patients with Cervical dystonia who have never received previously a botulinum toxin product. 104 botulinum toxin naïve CD patients will be studied.

The CPMP agreed with the post marketing study proposed by the Applicant.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of NeuroBloc was favourable in the following indication: NeuroBloc is indicated for the treatment of cervical dystonia (torticollis).

Medicinal product no longer authorised