NEUROBLOC (BOTULINUM TOXIN TYPE B)  
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NeuroBloc 5000 U/ml solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 5000 U Botulinum Toxin Type B.  
NeuroBloc 5000U/ml contains less than 1 mmol sodium per ml.  
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.  
Clear and colourless to light yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

See Section 5.1 for data on efficacy in patients responsive / resistant to Botulinum Toxin Type A.

4.2 Posology and method of administration

NeuroBloc should only be administered by intramuscular injection by a medical specialist with experience in the treatment of cervical dystonia and in the use of botulinum toxins.

The dosage units are specific to NeuroBloc and are not interchangeable with those used to quantify the dose of other botulinum toxin products.

The dose and frequency of administration should be adjusted for each patient depending on the clinical response. The initial dose is 10,000 U and should be divided between the two to four most affected muscles. 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. Therefore an initial dose of 5000 U may also be considered but a dose of 10,000 U may increase the likelihood of clinical benefit.

Care should be taken to ensure that NeuroBloc is not injected into a blood vessel.

NeuroBloc may be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection.

Injections should be repeated as required to maintain good function and minimise pain. In clinical studies 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%).
Adults (including the elderly ≥65 years old)
The dose recommended for cervical dystonia is applicable to adults of all ages, including the elderly.

For patients with reduced muscle mass the dose should be adjusted according to individual patient need.

Children and Adolescents
The safety and efficacy of NeuroBloc have not been demonstrated in children. NeuroBloc is not recommended in children and adolescents until further data become available.

Hepatic and renal impairment
Studies have not been carried out in patients with hepatic or renal impairment. However, the pharmacological characteristics do not indicate any need to adjust the dose.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

Individuals with other known neuromuscular diseases (e.g. ALS or peripheral neuropathy) or known neuromuscular junctional disorders (e.g. myasthenia gravis or Lambert-Eaton syndrome) should not be given NeuroBloc.

4.4 Special warnings and precautions for use
NeuroBloc is recommended for intramuscular administration only. Particular caution should be paid to ensure that it is not injected into a blood vessel.

Following repeated administration of NeuroBloc, development of an immune response can occur due to production of neutralising antibodies to Botulinum Toxin Type B. Tolerance, thought to be due to the development of an immune response, may occur uncommonly.

As with all injected medicines, caution should be used in patients with bleeding disorders or receiving anticoagulant therapy.

Neuromuscular effects related to spread of toxin, distant from the site of administration have been reported (see section 4.8).

Patients treated with therapeutic doses may experience exaggerated muscle weakness. There have been spontaneous reports of dysphagia, aspiration pneumonia and/or potentially fatal respiratory disease, after treatment with botulinum toxin type A/B.

Patients with underlying neuromuscular disorders including swallowing disorders are at increased risk of these undesirable effects. In patients with neuromuscular disorders or history of dysphagia and aspiration, botulinum toxins should be used under close medical supervision and only if the benefit clearly outweighs the risk.

Following NeuroBloc treatment, all patients and caregivers should be advised to seek medical attention for respiratory difficulties, choking or any new or worsening dysphagia.

Dysphagia has been reported following injection to sites other than the cervical musculature.
NeuroBloc contains human albumin. When medicinal products derived from human blood or plasma are administered, the possibility of transmitting infectious agents cannot be totally excluded. To reduce the risk of transmission of infective agents, stringent controls are applied to the selection of blood donors and donations. In addition, virus inactivation procedures are included in the production process.

The initial starting dose of 10,000 U (or 5000 U) is relevant only to NeuroBloc (Botulinum Toxin Type B). These dosage units are specific to NeuroBloc only and are not relevant to preparations of Botulinum Toxin Type A. The unit dose recommendations for Botulinum Toxin Type A are significantly lower than those for NeuroBloc and administration of Botulinum Toxin Type A at the unit dose recommended for NeuroBloc may result in systemic toxicity and life-threatening clinical sequelae.

### 4.5 Interactions with other medicinal products and other forms of interaction

The effect of administering different botulinum neurotoxin serotypes concurrently is unknown. However, in clinical trials, NeuroBloc was administered 16 weeks after the injection of Botulinum Toxin Type A.

Co-administration of NeuroBloc and aminoglycosides or agents interfering with neuromuscular transmission (e.g. curare-like compounds) should be considered with caution.

### 4.6 Pregnancy and lactation

Animal studies are insufficient with respect to effects on pregnancy and embryonal/foetal development. The potential risk for humans is unknown. NeuroBloc should not be used during pregnancy unless clearly necessary.

It is unknown whether Botulinum Toxin Type B is excreted in human breast milk. The excretion of Botulinum Toxin Type B in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with NeuroBloc should be made taking into account the benefit of breast-feeding to the child and the benefit of NeuroBloc therapy to the women.

### 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, the pharmacological characteristics do not indicate that they would be affected.

### 4.8 Undesirable effects

Undesirable effects, typically dry mouth, dysphagia and blurred vision, may occur following NeuroBloc injection. The two most commonly reported undesirable effects in clinical studies among patients with prior Botulinum Toxin Type A exposure were dry mouth and dysphagia, which were reported at a frequency of 41% and 29%, respectively. Data from clinical studies indicate that there is a tendency for the proportion of treatments associated with dysphagia to increase with higher doses injected into the sternocleidomastoid muscle. Injection site pain was also reported.

The two most commonly reported undesirable effects in a Phase IV comparative clinical study among toxin naïve patients treated with NeuroBloc 10,000 U to 15,000 U were dry mouth and dysphagia, which were reported at a frequency of 44% and 35%, respectively.
Adverse reactions seen in all trials are listed below according to MedDRA system organ class and in decreasing frequency which is defined as follows: Very Common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1000 to <1/100).

### Patients with Prior Botulinum Toxin Type A Exposure

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>dry mouth</td>
<td>torticollis (worsening from baseline), taste perversion</td>
</tr>
<tr>
<td>Respiratory thoracic and mediastinal disorders</td>
<td>voice alteration</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>dysphagia</td>
<td>dyspepsia</td>
</tr>
<tr>
<td>Musculoskeletal connective tissue and bone disorders</td>
<td>myasthenia</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>injection site pain</td>
<td>neck pain</td>
</tr>
</tbody>
</table>

### Patients Naïve to Botulinum Toxins

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>dry mouth, headache</td>
<td>torticollis</td>
</tr>
<tr>
<td>Eye disorders:</td>
<td></td>
<td>blurred vision</td>
</tr>
<tr>
<td>Respiratory thoracic and mediastinal disorders</td>
<td>dysphonia</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>dysphagia</td>
<td>dyspepsia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>injection site pain</td>
<td></td>
</tr>
</tbody>
</table>

In common with Botulinum Toxin Type A, electrophysiological jitter, which is not associated with clinical weakness or other electrophysiological abnormalities, may be experienced in some distant muscles.

**Post marketing experience**
Side effects related to spread of toxin distant from the site of administration have been reported (exaggerated muscle weakness, dysphagia, aspiration pneumonia with fatal outcome in some cases) (see section 4.4).

The following effects have also been reported during post marketing use: abnormal accommodation, ptosis, vomiting, constipation, flu-like symptoms, and asthenia.

### 4.9 Overdose

Cases of overdose (some with signs of systemic toxicity) have been reported. In the event of an overdose, general medical supportive measures should be instituted. Doses of up to 15,000 U have infrequently resulted in clinically significant systemic toxicity in adults. However, in children (non-approved use) clinically significant systemic toxicity has occurred at doses approved for the treatment of adult patients. If botulism is clinically suspected, hospitalisation for the monitoring of respiratory function (incipient respiratory failure) may be required.

In the event of an overdose or injection into a muscle that normally compensates for the cervical dystonia, it is conceivable that the dystonia may worsen. As with other botulinum toxins spontaneous recovery will occur over a period of time.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: muscle relaxant, peripherally acting agent, ATC code: M03A X 01

NeuroBloc is a neuromuscular blocking agent. The mechanism of action of NeuroBloc in blocking neuromuscular conduction occurs by a three-step process:

1. Extracellular binding of the toxin to specific acceptors on motor nerve terminals
2. Internalisation and release of the toxin into the cytosol of the nerve terminals
3. Inhibition of acetylcholine release from nerve terminals at the neuromuscular junction

When injected directly into a muscle, NeuroBloc causes a localised paralysis that gradually reverses over time. The mechanism by which muscle paralysis is reversed over time remains unknown, but may be associated with the intraneuronal turnover of the affected protein and/or sprouting of the nerve ending.

Two Phase III randomised, multicentre, double-blind, placebo-controlled studies were conducted in patients with cervical dystonia. Both studies enrolled adult patients (≥ 18 years) who had a history of receiving Botulinum Toxin Type A. The first study enrolled patients who were clinically resistant to type A toxin (A-non responders), confirmed by a Frontalis Type A test. The second study enrolled patients who continued to respond to type A toxin (A-responders). On enrolment all patients had Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) -Total scores of 20 or greater with at least two muscles involved, no neck contractures or other causes of decreased neck range of motion, and no history of any other neuromuscular disorder. The TWSTRS is comprised of three sub-scales which examine severity, pain and disability.

In the first study, type A resistant patients (A-non responders) were randomised to receive placebo or 10,000 U of NeuroBloc and in the second, type A toxin responsive patients (A-responders) were randomised to receive placebo, 5000 U or 10,000 U of toxin. Study drug was injected on a single occasion into 2 to 4 of the following muscles: splenius capitus, sternocleidomastoid, levator scapulae, trapezius, semispinalis capitus and scalene. The total dose was divided between the selected muscles and 1 to 5 injections per muscle were administered. There were 77 subjects enrolled into the first study and 109 into the second. Patient evaluations continued for 16 weeks post injection.

The primary efficacy outcome variable for both studies was the TWSTRS-Total score (range of possible scores is 0-87) at Week 4. The secondary endpoints included Visual Analogue Scales (VAS) to quantify the Patient Global Assessment of change and the Physician Global Assessment of change, both from baseline to Week 4. On these scales, scores of 50 indicate no change, 0 much worse, and 100 much better. Results of comparisons of the primary and secondary efficacy variables are summarised in Table 1. Analysis of the TWSTRS sub scales revealed significant effects on the severity of cervical dystonia and its associated pain and disability.

Exploratory analyses of these studies suggested that the majority of patients who showed a beneficial response by the fourth week had returned to their baseline status between 12 to 16 weeks after their injection.
Table 1:
Efficacy Results from Phase III NeuroBloc Studies

<table>
<thead>
<tr>
<th>Assessments</th>
<th>STUDY 1 (A-Resistant Patients)</th>
<th>STUDY 2 (A-Responsive Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo 10,000 U</td>
<td>Placebo 5000 U 10,000 U</td>
</tr>
<tr>
<td></td>
<td>n = 38 n = 39</td>
<td>n = 36 n = 36 n = 37</td>
</tr>
<tr>
<td>TWSTRS-Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean At Baseline</td>
<td>51.2 52.8</td>
<td>43.6 46.4 46.9</td>
</tr>
<tr>
<td>Mean at Week 4</td>
<td>49.2 41.8</td>
<td>39.3 37.1 35.2</td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>-2.0 -11.1</td>
<td>-4.3 -9.3 -11.7</td>
</tr>
<tr>
<td>P-Value*</td>
<td>0.0001</td>
<td>0.0115 0.0004</td>
</tr>
<tr>
<td>Patient Global</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean at Week 4</td>
<td>39.5 60.2</td>
<td>43.6 60.6 64.6</td>
</tr>
<tr>
<td>P-Value*</td>
<td>0.0001</td>
<td>0.0010 0.0001</td>
</tr>
<tr>
<td>Physician Global</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean at Week 4</td>
<td>47.9 60.6</td>
<td>52.0 65.3 64.2</td>
</tr>
<tr>
<td>P-Value*</td>
<td>0.0001</td>
<td>0.0011 0.0038</td>
</tr>
</tbody>
</table>

* Analysis of covariance, two-tailed tests, $\alpha = 0.05$

A further exploratory analysis of duration of effect employed data from a Phase II study in addition to the Phase III data described. 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 doses of 5000 and 10,000 U.

Table 2:
Duration of Effect in Responders

<table>
<thead>
<tr>
<th>Dose</th>
<th>4 Weeks</th>
<th>8 Weeks</th>
<th>12 Weeks</th>
<th>16 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>5000 U</td>
<td>43</td>
<td>22</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>10,000 U</td>
<td>38</td>
<td>34</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Overall</td>
<td>40</td>
<td>30</td>
<td>16</td>
<td>14</td>
</tr>
</tbody>
</table>

In open-label studies, doses up to 15,000 U were given to patients at intervals of not less than 12 weeks. The proportion of patients who responded to these injections was similar to that in the key controlled studies.

A Phase IV randomised, multicentre, double-blind study was conducted to compare the efficacy of NeuroBloc (10,000 U) to Botulinum Toxin Type A (150 U) in patients with cervical dystonia who have never previously received a botulinum toxin product. Final analysis was carried out on a total of 93 enrolled botulinum naive patients (46 in the NeuroBloc group) following a single injection, into 2 of 4 predetermined muscles. Baseline assessments, including TWSTRS and VAS pain evaluation by patient and investigator, were repeated at 4, 8 and 12 weeks after treatment.

The primary efficacy analysis demonstrates the noninferiority of NeuroBloc to Type A toxin as shown by the TWSTRS total score at session 1, week 4, for the PP population. Excluding site 121, the mean scores for NeuroBloc and Type A toxin were 32.7 (SD 11.61) and 36.0 (SD 11.71) respectively with a 95% CI of 29.3, 36.2 and 32.6, 39.4 respectively. The upper limit of the 1-sided CI in the LS mean difference (NeuroBloc - type A toxin) in the TWSTRS total
score at week 4 of session 1 for the PP population (excluding site 121) was 0.6 which is well within the predefined criterion for noninferiority of 4 points in the mean difference between groups adjusted for baseline for the TWSTRS. These findings led to an identical conclusion when site 121 was included.

The robustness of this analysis was confirmed by additional analyses that calculated the 1-sided 97.5% CI, analyses using the unadjusted scores, and analyses using the ITT and interim CSR PP populations. In this regard the noninferiority of NeuroBloc compared to Botulinum Toxin Type A is also supported by a responder analysis using the ITT population, which showed that a similar percentages of subjects showed any improvement in the TWSTRS score at Week 4 of Session 1 (86% NeuroBloc and 85% Botox), as did subjects who experienced at least a 20% decrease from baseline in the TWSTRS score at Week 4 of Session 1 (51% NeuroBloc, 47% Botox).

A Phase IV open label study has been conducted to evaluate the safety, immunogenicity and effect of repeated doses of NeuroBloc in subjects with cervical dystonia (CD) who were previously treated with Botulinum Toxin Type A. The primary objectives of the open label study were to evaluate the safety, immunogenicity and effect of repeat doses of NeuroBloc in subjects with CD who were already resistant to Botulinum Toxin Type A compared to subjects who were responsive to Botulinum Toxin Type A. A total of 130 subjects were enrolled, comprising 67 Type A resistant and 63 type A responsive. Subjects were given a starting dose of 10,000 Units of NeuroBloc at their first treatment, then subsequent doses modified at increments of 2,500 or 5,000 units to a maximum of 25,000 units with a dosage interval of at least 12 weeks.

Eight of the 67 Type A resistant subjects (11.9%) had developed neutralising antibodies to Botulinum Toxin Type B within completion of 4 treatment cycles of NeuroBloc and 15 out of 67 subjects (22.4%) had developed neutralising antibodies at the time of interim study analysis. The earliest development of neutralising antibodies was seen in 2 out of 67 subjects (3%) 6-9 months after the start of NeuroBloc treatment.

NeuroBloc treatment was associated with a low incidence of development of neutralising antibodies to Botulinum Toxin Type B during the first year of treatment. The presence of antibodies does not necessarily mean resistance to treatment as the number of patients truly resistant is likely to be much lower than the results indicate. Therefore patients resistant to Botulinum Toxin Type A may benefit from treatment with NeuroBloc and continue to experience this benefit over a long time period.

5.2 Pharmacokinetic properties

NeuroBloc injected intramuscularly produces localised muscle weakness by chemical denervation. Following local intramuscular injection of NeuroBloc serious adverse events that may have been due to systemic effects of Botulinum Toxin Type B, were observed in 12% of adverse drug reaction cases reported during the post-marketing experience (including the following adverse events: dry mouth, dysphagia and blurred vision). However, no pharmacokinetic or Absorption, Distribution, Metabolism and Excretion (ADME) studies have been performed.

5.3 Preclinical safety data

Single dose pharmacology studies in cynomolgus monkeys have shown no effects other than the anticipated dose-dependent paralysis of injected muscles, together with some diffusion of toxin at high doses producing similar effects in neighbouring non-injected muscles.
Single dose intramuscular toxicology studies have been performed in cynomolgus monkeys. The systemic No Observed Effect Level (NOEL) was shown to be approximately 960 U/kg. The dose resulting in death was 2400 U/kg.

Because of the nature of the product, no animal studies have been carried out to establish the carcinogenic effects of NeuroBloc. Standard tests to investigate the mutagenicity of NeuroBloc have not been performed.

Development studies in rats and rabbits have shown no evidence of foetal malformations or changes to fertility. In the development studies, the No Observed Adverse Effect Dose Level (NOAEL) in rats was 1000 U/kg/day for maternal effects and 3000 U/kg/day for foetal effects. In rabbits, the NOAEL was 0.1 U/kg/day for maternal effects and 0.3 U/kg/day for foetal effects. In the fertility studies the NOAEL was 300 U/kg/day for general toxicity in both males and females and 1000 U/kg/day for fertility and reproductive performance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium succinate
Sodium chloride
Human serum albumin (containing sodium caprylate and sodium acetyltryptophanate as excipients)
Hydrochloric acid for pH adjustment
Water for injections

6.2 Incompatibilities

In the absence of incompatibility studies, NeuroBloc must not be mixed with other medicinal products.

6.3 Shelf life

The shelf-life of the medicinal product as packaged for sale is 3 years.

Chemical and physical in-use stability has been demonstrated for 8 hours at 25°C for undiluted NeuroBloc.

From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the container in the outer carton in order to protect from light.

Vials may be stored for up to 8 hours at 25°C.
For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

NeuroBloc is supplied in 3.5 ml Type I glass vials, with siliconised grey butyl rubber stoppers oversealed by aluminium crimped caps.

Carton containing a single vial containing 0.5 ml, 1.0 ml or 2.0 ml of solution.

6.6 Special precautions for disposal and other handling

NeuroBloc is provided as a clear and colourless to light yellow sterile injectable solution in vials for single use only. Any unused solution should be discarded (see instructions below). Vials should be visually inspected prior to use. If the NeuroBloc solution is not clear and colourless/light yellow or if the vial appears damaged the product should be discarded as Medical Biohazardous Waste in accordance with local requirements.

The solution in the vials is ready for use.

NeuroBloc may be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection.

Do not shake.

Decontaminate any spill with 10% caustic solution, or sodium hypochlorite (household chlorine bleach – 2 ml (0.5%): 1 litre water) solution. Wear waterproof gloves and soak up the liquid with an appropriate absorbent. Place the absorbed toxin in an autoclave bag, seal it and process as Medical Biohazardous Waste in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eisai Limited
3 Shortlands
London
W6 8EE
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/166/001 – 2500 U
EU/1/00/166/002 – 5000 U
EU/1/00/166/003 – 10,000 U

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 January 2001
Date of latest renewal: 22 January 2006
10. DATE OF REVISION OF THE TEXT

26 February 2008

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

11. LEGAL CATEGORY
POM – medicinal product subject to medical prescription