ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NeuroBloc 5000 U/ml solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5000 U/ml Botulinum Toxin Type B.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Vial containing a 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

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

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 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 0.9% w/v sodium chloride 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%).

<u>Adults (including the elderly ≥65 years old)</u>
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 (<18 years old)
The safety and efficacy of NeuroBloc have not been demonstrated in children.

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 and should only be injected by medical specialists with experience of the treatment of cervical dystonia and the use of botulinum toxins. 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 trials 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. Adverse reactions seen in all trials are listed below according to organ class and frequency which is defined as follows: Very Common (>1/10); Common (>1/100, <1/10); Uncommon (>1/1000, <1/100).

Nervous System – Very Common: dry mouth; Common: torticollis (worsening from baseline)

Body As A Whole – Very Common: injection site pain; Common: neck pain

Digestive System – Very Common: dysphagia; Common: dyspepsia

Respiratory System – Common: voice alteration

Musculoskeletal System – Common: myasthenia

Special Senses – Common: taste perversion

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 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: MO3A 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

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

* 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

Dose	Duration Of Effect (% Responders)			
	4 Weeks	8 Weeks	12 Weeks	16 Weeks
5000 U	43	22	16	19
10,000 U	38	34	16	11
Overall	40	30	16	14

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 study has been conducted to demonstrate the non-inferiority of NeuroBloc to botulinum toxin type A in patients with cervical dystonia who have never previously received a botulinum toxin product. An interim analysis has been carried out on the total of 111 enrolled botulinum naive enrolled patients (56 in the NeuroBloc group) following a single injection, into 2 of 4 predetermined muscles, of NeuroBloc 10,000 units or botulinum toxin type A 150 units. Baseline assessments including TWSTRS and VAS pain evaluation by patient and investigator were repeated at 4, 8 and 12 weeks after treatment. The effects of both treatments were essentially the same at each time-point up to 12 weeks (Table 3).

The analysis showed that there are no clinically relevant differences between these two treatments. The primary analysis of non-inferiority was not proven (90% CI of difference –2.66, 4.01 compared with an upper limit of <4.00), however, sensitivity analysis for robustness and the confirmatory ITT population analysis (90% CI of difference –3.4, 3.2 and –3.23, 2.98 respectively) suggest there is no clinically relevant difference between the two products.

Table 3: Summary of TWSTRS – total score at all visits: Treatment 1 (PP population)

Visit	Statistic	Treatment	
		NeuroBloc	Botulinum toxin type A
Day 0	n: mean (SD)	41: 44.9 (11.3)	48: 45.3 (10.8)
Week 4	n: mean (SD)	41: 33.2 (10.8)	48: 32.8 (11.0)
Week 8	n: mean (SD)	37: 33.5 (11.9)	47: 32.5 (13.0)
Week 12	n: mean (SD)	32: 39.7 (12.5)	43: 39.7 (16.3)

A Phase IV open label study has been conducted to evaluate the safety and immunogenicity of repeated doses of NeuroBloc in subjects with cervical dystonia who were resistant to Botulinum Toxin Type A. The primary objective of the study was to evaluate immunogenicity in subjects who were already resistant to Botulinum-Toxin Type A, in other words, a group that is enriched for subjects that may be early neutralising antibody formers. A total of 67 Type-A resistant patients were enrolled and 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. An interim analysis was performed when at least 50 subjects has received an average of at least 4 treatments cycles.

Eight of the 67 Type A resistant subjects (11.9%) within completion of 4 treatment cycles of NeuroBloc and 15/67 (22.4%) subjects at the time of study analysis had developed neutralising

antibodies to Botulinum Toxin Type B. The earliest development of neutralising antibodies was seen in 2/67 (3%) subjects 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 studiesthe 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 andsodium 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 room temperature 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^{o}C - 8^{o}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 room temperature.

For storage conditions of diluted NeuroBloc see section 6.3.

6.5 Nature and contents of container

NeuroBloc is supplied in 3.5 ml Type I glass vials, with siliconised 13 mm grey butyl rubber stoppers oversealed by 13 mm aluminium crimped caps.

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

The solution is clear and colourless to light yellow.

6.6 Special precautions for disposal

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 0.9% w/v sodium chloride 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.

Due to the special nature of NeuroBloc, used vials, needles and syringes must be processed as Medical Biohazardous Waste in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Solstice Neurosciences Ltd
Fitzwilton House
Wilton Place
Dublin 2
Ireland.

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 last renewal: 6 April 2006

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Solstice Neurosciences Inc
701 Gateway Blvd, South San Francisco
California 94080
USA

Name and address of the manufacturer responsible for batch release

Almac Pharma Services Ltd.
Almac House
20 Seagoe Industrial Estate,
Craigavon BT63 5QD
United Kingdom

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not aplicable.

- **OTHER CONDITIONS**

The marketing Authorisation holder will continue to submit periodic safety update reports on a 3 year cycle.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON OUTER PACKAGING
0.5 ml vial

1. NAME OF THE MEDICINAL PRODUCT

NeuroBloc
5000 U/ml Solution for injection
Botulinum Toxin Type B

2. STATEMENT OF ACTIVE SUBSTANCES

Composition:
5000 U/ml Botulinum Toxin Type B (2500 U per vial)

3. LIST OF EXCIPIENTS

Disodium succinate, sodium chloride, human serum albumin, sodium caprylate,.sodium acetyltryptophanate, hydrochloric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 x 0.5 ml vial, 2500 U

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.

Read the package leaflet before use.

6. SPECIAL WARNINGS THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP: MM-YYYY

9. SPECIAL STORAGE PRECAUTIONS

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

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIAL DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Read package leaflet for special precautions for handling and disposal.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Solstice Neurosciences Ltd.
Fitzwilton House
Wilton Place
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/166/001

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[Not applicable.]

16. BRAILLE

[Not applicable]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
0.5 ml vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

NeuroBloc
IM

2. METHOD OF ADMINISTRATION

Solution for Injection

3. EXPIRY DATE

EXP: MM-YYYY

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, VOLUME OR BY UNIT

2500 U

PARTICULARS TO APPEAR ON OUTER PACKAGING
1.0 ml vial

1. NAME OF THE MEDICINAL PRODUCT

NeuroBloc
5000 U/ml Solution for injection
Botulinum Toxin Type B

2. STATEMENT OF ACTIVE SUBSTANCES

Composition:
5000 U/ml Botulinum Toxin Type B (5000 U per vial)

3. LIST OF EXCIPIENTS

Disodium succinate, sodium chloride, human serum albumin, sodium caprylate, sodium acetyltryptophanate, hydrochloric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 x 1.0 ml vial, 5000 U

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.

Read the package leaflet before use.

6. SPECIAL WARNINGS THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP: MM-YYYY

9. SPECIAL STORAGE PRECAUTIONS

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

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIAL DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Read package leaflet for special precautions for handling and disposal.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Solstice Neurosciences Ltd.
Fitzwilton House
Wilton Place
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/166/002

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[Not applicable.]

16. BRAILLE

[Not applicable]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
1.0 ml vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

NeuroBloc
IM

2. METHOD OF ADMINISTRATION

Solution for Injection

3. EXPIRY DATE

EXP: MM-YYYY

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, VOLUME OR BY UNIT

5000 U

PARTICULARS TO APPEAR ON OUTER PACKAGING
2.0 ml vial

1. NAME OF THE MEDICINAL PRODUCT

NeuroBloc
5000 U/ml Solution for injection
Botulinum Toxin Type B

2. STATEMENT OF ACTIVE SUBSTANCES

Composition:
5000 U/ml Botulinum Toxin Type B (10,000 U per vial)

3. LIST OF EXCIPIENTS

Disodium succinate, sodium chloride, human serum albumin,sodium caprylate, sodium acetyltryptophanate, hydrochloric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 x 2.0 ml vial, 10,000 U

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.

Read the package leaflet before use.

6. SPECIAL WARNINGS THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP: MM-YYYY

9. SPECIAL STORAGE PRECAUTIONS

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

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIAL DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Read package leaflet for special precautions for handling and disposal.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Solstice Neurosciences Ltd.
Fitzwilton House
Wilton Place
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/166/003

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[Not applicable.]

16. BRAILLE

[Not applicable]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
2.0 ml vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

NeuroBloc
IM

2. METHOD OF ADMINISTRATION

Solution for Injection

3. EXPIRY DATE

EXP: MM-YYYY

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, VOLUME OR BY UNIT

10,000 U

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
NeuroBloc 5000 U/ml Solution for Injection
Botulinum Toxin Type B

Read all of this leaflet carefully before you are given this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. WHAT NEUROBLOC IS AND WHAT IT IS USED FOR

NeuroBloc is a toxin produced by bacteria called *Clostridium botulinum*.

NeuroBloc reduces the release of the 'chemical messenger', acetylcholine, which is made by nerves and tells your muscles to contract. If nerves are prevented from releasing this messenger, abnormal muscle contractions may be reduced or completely stopped.

NeuroBloc is used to treat cervical dystonia (torticollis). If you have cervical dystonia, you experience contractions of the neck and/or shoulder muscles that you cannot control.

2. BEFORE YOU ARE GIVEN NEUROBLOC

Tell your doctor:
- if you are allergic to any of the ingredients in this medicine
- if you suffer from a disease of the nerves or muscles especially one causing muscle weakness
- if you are pregnant or breast-feeding

as you should not receive NeuroBloc in these cases.

Also tell you doctor:
- if you suffer from a bleeding disorder such as haemophilia
- when you are receiving medication such as warfarin, to prevent your blood clotting.
- if you have lung problems
- if you have any difficulty swallowing before or after your NeuroBloc injection. Rarely severe swallowing problems can result in breathing food or liquids into your lungs and cause pneumonia which might be fatal.

NeuroBloc is not approved for use in children. You should not normally be given NeuroBloc if you are under 18 years old.

Taking other medicines:

Please tell your doctor if you are taking antibiotics for an infection. If you are going to have an operation, please tell your doctor if you have been given NeuroBloc as it can interfere with drugs you may be given before a general anaesthetic.

Also inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Pregnancy and breast feeding:
Generally, you should not be given NeuroBloc if you are pregnant or breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:
If you feel tired, have any loss of sensation or blurred vision, take care when driving or operating machinery.

Important information about some of the ingredients of NeuroBloc:
NeuroBloc contains a very small amount of albumin which comes from human blood. It is very unlikely that this could pass on an infection but it cannot be entirely ruled out.

3. HOW YOU WILL BE GIVEN NEUROBLOC

Your doctor will decide how much NeuroBloc to give you. The dose will usually be 10,000 Units, but it can be higher or lower, depending on your doctor's decision and your response to any previous injections of NeuroBloc.

If you have the impression that the effect of NeuroBloc is too strong or too weak, talk to your doctor.

NeuroBloc will be injected into your neck and/or shoulder muscles, depending on which ones are causing the problem. Your doctor will decide into which muscles to inject NeuroBloc and may inject part of the dose into different places in the muscles.

The effects of NeuroBloc will usually wear off after approximately 12 to 16 weeks. Your doctor will decide when you need another injection and how much to give you.

You can continue injections of NeuroBloc as long as it gives you relief from your symptoms. After you have had a number of injections, your body may produce antibodies that may make the treatment less effective. Your doctor knows about this and will look for signs of it.

If you are given more NeuroBloc than you need, some of your muscles that were not injected may feel weak. If this happens you should speak to your doctor immediately. Tell your doctor immediately if you have difficulty breathing. If he/she is unavailable seek emergency assistance.

If you forget to visit your doctor to receive your injection:
The effects of NeuroBloc will gradually wear off and the abnormal muscle contractions may come back.

4. POSSIBLE SIDE EFFECTS

Like all medicines, NeuroBloc can cause side effects, although not everybody gets them. You may feel pain at the place where you had the injection but this should wear off after a few minutes.

Effects may be seen in other areas than where you have received the injection and may occur days to weeks after injection. You may find that your mouth feels dry and/or that swallowing becomes difficult. In rare cases difficulty in swallowing may be severe and choking is possible. If you develop new or worsening swallowing difficulty, choking or breathing problems seek medical help immediately.

You may notice one or more of the following effects after injection:
- weakness, pain or muscle stiffness around your body
- neck pain
- indigestion
- changes in the taste of your food and drink
- changes in the sound of your voice.
- blurred vision
- drooping of the upper eyelid
- vomiting
- constipation
- flu-like symptoms
- loss of strength or energy

It is also possible that torticollis (turning of your head which you cannot control) could become worse after you have had your injection.

If any of the side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NEUROBLOC

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the carton.

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

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

NeuroBloc may be stored for up to 8 hours at room temperature.

6. FURTHER INFORMATION

What NeuroBloc contains

- The active substance is Botulinum Toxin Type B.

- The other ingredients are disodium succinate, sodium chloride, human serum albumin (containing sodium caprylate and sodium acetyltryptophanate as excipients), hydrochloric acid (for pH adjustment) and water for injections.

- The medicinal product contains less than 1 mmol sodium (23 mg) per 10,000 units of NeuroBloc, i.e. essentially “sodium free”.

What NeuroBloc looks like and contents of the pack.

NeuroBloc is a clear and colourless to pale yellow solution supplied in a glass vial that contains 0.5ml (2500Units), 1.0ml (5000 Units) or 2.0ml (10,000 Units) of solution for injection.

Marketing Authorisation holder and Manufacturer

The Marketing Authorisation holder is:

Solstice Neurosciences Ltd
Fitzwilton House
Wilton Place
Dublin 2
Ireland

The Manufacturer is:

Almac Pharma Services Ltd.
Almac House
20 Seagoe Industrial Estate
Craigavon
BT63 5QD
United Kingdom

This leaflet was last approved in:

The following information is intended for medical or healthcare professionals only

INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

The solution in the vials is ready for use.

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.

NeuroBloc may be diluted with 0.9% w/v sodium chloride 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.

Due to the special nature of NeuroBloc, used vials, needles and syringes must be processed as Medical Biohazardous Waste in accordance with local requirements.

ANNEX IV

GROUNDS FOR ONE ADDITIONAL RENEWAL

Based upon the data that have become available since the granting of the initial marketing authorisation, the benefit/risk balance of Neurobloc remains positive, but its safety profile should be monitored closely for the following reason.
There is an overall concern for the class of botulinum toxins regarding dysphagia and fatal outcomes. This is not specific to Neurobloc but concerns the whole class.
Therefore, considering the above-mentioned safety concern, the CHMP recommended one additional renewal for Neurobloc.