

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125274Orig1s000

REMS

BLA STN 125274 AND 125286 DYSPORT™ (ABOBOTULINUMTOXINA)

Acetylcholine release inhibitor and neuromuscular blocking agent

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NEW PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I GOAL(S)

DYSPORT™ (abobotulinumtoxinA) is a botulinum toxin product that acts as an acetylcholine release inhibitor and neuromuscular blocking agent. The potency units of DYSPORT are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of DYSPORT™ cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

The goal of the REMS is to ensure that the potential benefits of treatment with DYSPORT™ for the treatment of Cervical Dystonia and Glabellar Lines outweigh the potential risks of:

- Medication errors related to the lack of interchangeability of DYSPORT™ units with those of toxins of other manufacturers; and
- the potential for the occurrence of distant spread of toxin effect beyond the injection site discussed in the Warnings and Precautions section of the package insert.

II REMS ELEMENTS

The DYSPORT™ REMS includes a Medication Guide for patients and a Communication Plan which are further detailed below. The purposes of the REMS elements are to ensure that the potential benefits of treatment with DYSPORT™ for the treatment of Cervical Dystonia and Glabellar Lines outweigh the potential risks.

A Medication Guide

A Medication Guide will be dispensed with each DYSPORT™ prescription (see REMS Appendix 2).

DYSPOTM is available in cartons containing either a single or two 500 Unit vials of DYSPOTM or a single 300 Unit vial of DYSPOTM. The Medication Guide is inserted inside the carton with the vial(s) of DYSPO. A Medication Guide will be provided for each vial of DYSPOTM. The carton prominently states "Dispense the enclosed Medication Guide to each patient". Each Medication Guide is inspected to ensure that the correct version is being used and that the component is available for insertion into each carton of DYSPOTM.

Because the Medication Guide is included as part of the secondary package for DYSPOTM, IPSEN has met the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide.

B Communication Plan

Ipsen will implement a communication plan to healthcare providers to support the implementation of this REMS.

The primary objectives of this Communication Plan are to ensure that the potential risk of serious adverse reactions due to the distant spread of effect of botulinum toxin is minimized when DYSPOTM is being used in the approved indication for Cervical Dystonia and Glabellar Lines and to inform physicians of the lack of interchangeability of DYSPOTM units with those of toxins of other manufacturers.

Ipsen will provide a Dear Healthcare Provider Letter (See REMS Appendix 1) to healthcare professionals involved in the prescribing, dispensing, or administration of DYSPOTM. The Dear Healthcare Provider Letter will be distributed at launch of the approval of DYSPOTM to neurologists, dermatologists, and other specialties and healthcare professional staff who prescribe or inject DYSPOTM or other botulinum toxin products (i.e., physical medical and rehabilitation specialists, dermatologists, ophthalmologists and other specialists who have previously dispensed botulinum toxins).

C Elements to Assure Safe Use

The REMS for DYSPOTM does not require Elements to Assure Safe Use.

D Implementation System

The REMS for DYSPOTM does not require an Implementation System.

E Timetable for Submission of Assessments

Ipsen will continually review the success of the Communication Plan and make any changes necessary to ensure efficient communication of the potential risks to patients and treating physicians. In particular, the number and nature of reports of

undesirable effects, medication errors indicated by the lack of effect, overdose, etc. will be carefully monitored.

The estimated timetable for Submission of Assessments is as follows:

- 1st Assessment: 18 months from product launch
- 2nd Assessment: 3 years from product launch
- 3rd Assessment: 7 years from product launch

Ipsen will submit the assessments within 60 days of the close of the intervals as noted above.

DYSPOTMRT™ New Proposed REMS Appendix 1: Dear Healthcare Provider Letter**Dear Healthcare Provider Letter for the treatment of Cervical Dystonia**

Announcing the Approval of DYSPOTMRT™ (abobotulinumtoxinA)

Dear Healthcare Provider:

Ipsen Biopharm Limited, the makers of DYSPOTMRT™, and Tercica, Inc. the distributor of the product for medical use, would like to notify you that DYSPOTMRT™ has been approved for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients. DYSPOTMRT™ has also been approved for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients <65 years of age. DYSPOTMRT™ (abobotulinumtoxinA) is a botulinum toxin product that acts as an acetylcholine release inhibitor and neuromuscular blocking agent.

In order to ensure that the benefits of DYSPOTMRT™ treatment outweigh the potential risks of DYSPOTMRT™ treatment, a Risk Evaluation and Mitigation Strategy has been implemented. The goals of the Risk Evaluation and Mitigation Strategy are:

- to reduce the potential for medication errors related to the lack of interchangeability of DYSPOTMRT™ units with those of other botulinum toxin products from other manufacturers, and
- to communicate the potential for the distant spread of toxin effect beyond the injection site.

Non-Interchangeability of botulinum toxin Units:

It is important to note that the potency units of DYSPOTMRT™ are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of DYSPOTMRT™ cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

The approved DYSPOTMRT™ starting dose for the treatment of cervical dystonia in botulinum toxin-naïve and previously treated patients is 500 Units. Further doses of DYSPOTMRT™ to treat cervical dystonia should be given no less than 12 weeks apart. Depending on patient response, doses may be increased or decreased in 250 Unit increments. The maximum recommended dose for cervical dystonia is 1000 Units every 12 weeks.

The approved total dose of DYSPORT™ for the temporary improvement of glabellar lines is 50 Units given in 5 equal aliquots in naïve and previously treated patients. When used for retreatment, DYSPORT™ should be administered no more frequently than every 3 months.

When prescribing DYSPORT™ to your patients, please take care to appropriately document DYSPORT™'s unique established drug name "*abobotulinumtoxinA*" to reduce the potential for medication errors that may arise from confusion between botulinum toxins from different manufacturers.

Spread of Toxin Effect:

All botulinum toxins including DYSPORT™ have the potential to cause clinically detectable effects that occur in areas beyond and not contiguous with the site of injection. These effects are consistent with the pharmacological action of botulinum toxin. The risk of adverse events may be reduced by using the lowest effective dose and not exceeding the recommended dose for each indication.

Patients with, or at risk of, peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be closely supervised when treated with DYSPORT™.

Patients and/or their care partner should be informed of the potential risk of distant spread of botulinum toxin effect associated with the use of DYSPORT™. They should be instructed to recognize the early symptoms of toxicity (difficulty swallowing, breathing, or speaking) and urged to seek immediate medical advice if they experience any of them. Patients and/or their care partner should also be instructed to inform other healthcare providers about their use of botulinum toxin when being treated for other medical conditions.

Information on the Spread of Toxin Effect (Boxed Warning and section 5.2), Dysphagia and Breathing Difficulties in the Treatment of Cervical Dystonia (section 5.3), and Pre-Existing Neuromuscular Disorders (section 5.5) is provided in the enclosed copy of the FDA approved DYSPORT™ Full Prescribing Information as well as below.

Distant Spread of Toxin Effect

Postmarketing reports indicate that the effects of DYSPORT™ and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.

5 WARNINGS AND PRECAUTIONS**5.2 Spread of Toxin Effect**

Postmarketing safety data from DYSPORT™ and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of the symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, symptoms consistent with the spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia.

5.3 Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

Treatment with DYSPORT™ and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or

swallowing. When distant effects occur, additional respiratory muscles may be involved [see Warnings and Precautions (5.2)].

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several weeks, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been post marketing reports of serious breathing difficulties, including respiratory failure, in cervical dystonia patients.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin [see Warnings and Precautions (5.2) and Adverse Reactions (6.1)].

5.5 Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of DYSPOTM [see Adverse Reactions (6.1)].

Patient Medication Guide:

One of the elements of the Risk Evaluation and Mitigation Strategy is the FDA approved Patient Medication Guide. When discussing the risks above and other risks identified in the Full Prescribing Information with patients and/or their care partner, you must provide them with a copy of the Patient Medication Guide enclosed with each vial of DYSPOTM. The Patient Medication Guide and Full Prescribing Information are also available from your local Tercica, Inc. sales representative, on our website at www.dysport.com, or by calling 1-877-397-7671.

Finally, please remember to report suspected adverse reactions associated with DYSPOTM treatment at 1-877-397-7671 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

We look forward to serving you and your patients.

Best regards,

Tercica Inc.
Brisbane, CA

Dear Healthcare Provider Letter for the treatment of Glabellar lines

Announcing the Approval of DYSPORT™ (abobotulinumtoxinA)

Dear Healthcare Provider:

Ipsen Biopharm Limited, the makers of DYSPORT™, and Medicis Aesthetics, Inc. the distributor of the product for aesthetic use, would like to notify you that DYSPORT™ has been approved for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients <65 years of age. DYSPORT™ has also been approved for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients. DYSPORT™ (abobotulinumtoxinA) is a botulinum toxin product that acts as an acetylcholine release inhibitor and neuromuscular blocking agent.

In order to ensure that the benefits of DYSPORT™ treatment outweigh the potential risks of DYSPORT™ treatment, a Risk Evaluation and Mitigation Strategy has been implemented. The goals of the Risk Evaluation and Mitigation Strategy are:

- to reduce the potential for medication errors related to the lack of interchangeability of DYSPORT™ units with those of other botulinum toxin products from other manufacturers, and
- to communicate the potential for the distant spread of toxin effect beyond the injection site.

Non-Interchangeability of botulinum toxin Units:

It is important to note that the potency units of DYSPORT™ are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of DYSPORT™ cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

The approved total dose of DYSPORT™ for the temporary improvement of glabellar lines is 50 Units given in 5 equal aliquots in naïve and previously treated patients. When used for retreatment, DYSPORT™ should be administered no more frequently than every 3 months.

The approved DYSPORT™ starting dose for the treatment of cervical dystonia in botulinum toxin-naïve and previously treated patients is 500 Units. Further doses of DYSPORT™ to treat cervical dystonia should be given no less than 12 weeks apart. Depending on patient response, doses may be increased or decreased in 250 Unit

increments. The maximum recommended dose for cervical dystonia is 1000 Units every 12 weeks.

When prescribing DYSPOTM to your patients, please take care to appropriately document DYSPO's unique established drug name "*abobotulinumtoxinA*" to reduce the potential for medication errors that may arise from confusion between botulinum toxins from different manufacturers.

Spread of Toxin Effect:

All botulinum toxins including DYSPOTM have the potential to cause clinically detectable effects that occur in areas beyond and not contiguous with the site of injection. These effects are consistent with the pharmacological action of botulinum toxin. The risk of adverse events may possibly be reduced by using the lowest effective dose and not exceeding the recommended dose for each indication.

Patients with, or at risk of, peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be closely supervised when treated with DYSPOTM.

Patients and/or their care partner should be informed of the potential risk of distant spread of botulinum toxin effect associated with the use of DYSPOTM. They should be instructed to recognize the early symptoms of toxicity (difficulty swallowing, breathing, or speaking) and urged to seek immediate medical advice if they experience any of them. Patients and/or their care partner should also be instructed to inform other healthcare providers about their use of botulinum toxin when being treated for other medical conditions.

Information on the Spread of Toxin Effect (Boxed Warning and section 5.2), Dysphagia and Breathing Difficulties in the Treatment of Cervical Dystonia (section 5.3), and Pre-Existing Neuromuscular Disorders (section 5.5) is provided in the enclosed copy of the FDA approved DYSPOTM Full Prescribing Information as well as below.

Distant Spread of Toxin Effect

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Treatment with DYSPOTM and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or

swallowing. When distant effects occur, additional respiratory muscles may be involved [see Warnings and Precautions (5.2)].

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Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin [see Warnings and Precautions (5.2) and Adverse Reactions (6.1)].

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Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of DYSPOTM [see Adverse Reactions (6.1)].

Patient Medication Guide:

One of the elements of the Risk Evaluation and Mitigation Strategy is the FDA approved Patient Medication Guide. When discussing the risks above and other risks identified in the Full Prescribing Information with patients and/or their care partner, you must provide them with a copy of the Patient Medication Guide enclosed with each vial of DYSPOTM. The Patient Medication Guide and Full Prescribing Information are also available from your local Medicis Aesthetics, Inc. sales representative, on our website at www.DysportUSA.com, or by calling 1-877-397-7671.

Finally, please remember to report suspected adverse reactions associated with DYSPOTM treatment at 1-877-397-7671 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

We look forward to serving you and your patients.

Best regards,

Medicis Aesthetics, Inc.
Scottsdale, AZ