

## Ipsen announces FDA approval of Dysport® (abobotulinumtoxinA) for the treatment of lower limb spasticity in adults

**Spasticity may affect adults who suffer from stroke, traumatic brain injury, spinal cord injury, multiple sclerosis, and cerebral palsy**

**Paris (France), 16 June 2017** – Ipsen (Euronext: IPN; ADR: IPSEY) (Ipsen) today announced that the U.S. Food and Drug Administration (FDA) has expanded the approved use of Dysport® (abobotulinumtoxinA) for injection for the treatment of spasticity in adults, based on its supplemental Biologics License Application (sBLA) in lower limb spasticity. In July 2015, Dysport® was approved for the treatment of upper limb spasticity in adults. In July 2016, Dysport® was approved to treat pediatric patients with lower limb spasticity aged two and older, making it the first and only botulinum toxin that the FDA approved for this indication.

In a Phase III, multi-center, prospective, double-blind, randomized placebo-controlled study, adult patients treated with Dysport® following a stroke or traumatic brain injury showed improvement in muscle tone at the ankle joint, measured by the mean change from baseline on the Modified Ashworth Scale (MAS) at Week 4. The duration of response for the majority of patients within the study was between 12-16 weeks. In this study, some patients experienced a longer duration of response (approximately 20 weeks).

The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of Dysport® and muscles to be injected. Repeat Dysport® treatment should be administered when the effect of a previous injection has diminished, but no sooner than 12 weeks after the previous injection.

Lower limb spasticity impacts a person's movement. In adults, approximately one in three stroke patients, one in three patients with spinal cord injury, one in six patients with traumatic brain injury, and two in three patients with Multiple Sclerosis (MS) will develop lower limb spasticity.<sup>1,2</sup> Adult patients with Cerebral Palsy (CP) also commonly experience spasticity in their lower limbs.<sup>1</sup>

*“Adult patients who have developed spasticity as a result of a stroke, Multiple Sclerosis, Cerebral Palsy, spinal cord injury, or traumatic brain injury now have another option when seeking treatment that helps reduce the effects of the increased muscle tone in their lower extremities,”* said **Alexandre Lebeaut, MD, Executive Vice-President, R&D, Chief Scientific Officer, Ipsen.**

Dysport® and all botulinum toxin products have a Boxed Warning which states that the effects of the botulinum toxin may spread from the area of injection to other areas of the body, causing symptoms similar to those of botulism. Those symptoms include swallowing and breathing difficulties that can be life-threatening. Dysport® is contraindicated in patients with known hypersensitivity to any botulinum toxin preparation or to any of the components; or in the presence of infection at the proposed injection site(s); or in patients known to be allergic to cow's milk protein. 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. Please see below for additional Important Safety Information.

*“Dysport® is currently the only botulinum toxin approved by the FDA for the treatment of spasticity in adults in upper and lower limbs and also for the treatment of lower limb spasticity in children ages two and older,”* said **Cynthia Schwalm, Executive Vice-President and President, North America Commercial Operations, Ipsen.** *“We are proud that Dysport® is now available to support an additional population of patients—including those adults managing their spasticity associated with stroke, brain injury, spinal cord injury, Multiple Sclerosis, or Cerebral Palsy—and that Ipsen is able to provide comprehensive support offerings, including the IPSEN CARES® patient assistance program and the C.L.I.M.B.® injector training platform for healthcare providers.”*

### **About Spasticity**

Spasticity is a condition in which there is an abnormal increase in muscle tone or stiffness in one or more muscles, which might interfere with movement. Spasticity is usually caused by damage to nerve pathways in the brain or spinal cord that control muscle movement, and may occur in association with cerebral palsy, spinal cord injury, multiple sclerosis, stroke, and brain or head trauma.<sup>3</sup> In adults, approximately one in three stroke patients, one in three patients with spinal cord injury, one in six patients with traumatic brain injury, and two in three patients with MS will develop lower limb spasticity.<sup>1,2</sup>

Lower limb spasticity commonly involves spasticity in the gastrocnemius and soleus muscle complex located in the calf.<sup>4,5</sup> These calf muscles, during walking, work to raise the heel from the ground.<sup>4</sup> Symptoms of spasticity may include increased muscle tone, rapid muscle contractions, exaggerated deep tendon reflexes, and/or muscle spasms. The degree of spasticity can vary from mild muscle stiffness to severe, painful, and uncontrollable muscle spasms.<sup>3</sup>

### **About the Phase III Study**

The Phase III, multi-center, prospective, double-blind, randomized placebo-controlled study, sponsored by Ipsen, evaluated the efficacy and safety of Dysport® for the treatment of lower limb spasticity in a population of 381 adult patients (253 received Dysport® and 128 received placebo.) Patients had lower limb spasticity (MAS score >2 in the affected ankle joint for toxin naïve patients or MAS score >3 in the affected ankle joint for toxin non-naïve patients at least four months since the last botulinum toxin injection in the affected lower limb) and were at least six months post-stroke or post-traumatic brain injury.

Patients were randomized to Dysport® 1000 Units (N=125), Dysport® 1500 Units (N=128), or placebo (N=128) injected intramuscularly into the gastrocnemius-soleus muscle complex located in the calf. In the study, at least one additional lower limb muscle was injected, according to the clinical presentation. Some of the lower limb muscles injected during the study included: tibialis posterior, flexor digitorum longus, and/or flexor hallucis longus.

There was improvement in both the mean change from baseline in MAS score at the ankle joint at Week 4 [LS mean change from baseline on MAS treatment difference vs. placebo were: -0.5 for placebo, -0.6 for Dysport® 1000 Units (NS<sup>6</sup>), and -0.8 for Dysport® 1500 Units (p<0.05)].

The study concluded that Dysport® 1500 Units injection resulted in a statistically significant improvement in muscle tone and spasticity at the ankle joint. The duration of response for the



majority of patients within the study was between 12-16 weeks. In this study, some patients experienced a longer duration of response (approximately 20 weeks).

The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of Dysport® and muscles to be injected. Repeat Dysport® treatment should be administered when the effect of a previous injection has diminished, but no sooner than 12 weeks after the previous injection.

The most common adverse reactions (≥5% and greater than placebo in either Dysport® group) in adults with lower limb spasticity for Dysport® 1000 Units, Dysport® 1500 Units, and Placebo, respectively, were: falls (9%, 6%, 3%), muscular weakness (2%, 7%, 3%), pain in extremity (6%, 6%, 2%). Muscular weakness was reported more frequently in women (10%) treated with 1500 Units of Dysport® compared to men (5%).

### **About Dysport® (abobotulinumtoxinA) for Injection**

Dysport® is an injectable form of botulinum toxin type A (BoNT-A), which is isolated and purified from Clostridium bacteria producing BoNT-A. It is supplied as a lyophilized powder. Dysport® has approved indications in the United States for the treatment of adults with Cervical Dystonia (CD) and for the treatment of spasticity in adult patients. Dysport® is also the first and only FDA-approved botulinum toxin for the treatment of lower limb spasticity in pediatric patients two years of age and older.

The C.L.I.M.B.® (Continuum of Learning to Improve Management with Botulinum Toxin) injector training platform is a multi-tiered learning continuum designed to educate physicians with every level of experience with botulinum toxin therapy. C.L.I.M.B.® can help physicians improve their clinical skills involving the appropriate use of Dysport®. Visit [www.Dysport.com](http://www.Dysport.com) to learn more.

### **About IPSEN CARES® in the United States**

IPSEN CARES® (Coverage, Access, Reimbursement, & Education Support) is dedicated to ensuring patients, providers and caregivers have the resources needed to help access the Ipsen medications that are critical to managing their conditions. IPSEN CARES® is staffed Monday to Friday by experts who can assist with a broad range of medical, educational, logistical and coverage information regarding Ipsen medicines. Involving the entire treatment team that surrounds patients on a daily basis, IPSEN CARES® can provide benefits verification (research of a patient's medical or pharmacy benefit insurance coverage); prior authorization information; a patient assistance program (free medications for uninsured patients); co-pay assistance programs for eligible patients; billing and coding support; coordination with specialty pharmacies. Additional information is also available by visiting (<http://www.ipsencares.com>).

## **INDICATIONS AND IMPORTANT SAFETY INFORMATION (United States)**

### **INDICATIONS**

Dysport® (abobotulinumtoxinA) for injection is indicated for the treatment of:

- Spasticity in adult patients
- Adults with cervical dystonia
- Lower limb spasticity in pediatric patients 2 years of age and older.



The safety and effectiveness of Dysport® injected into upper limb muscles or proximal muscles of the lower limb for the treatment of spasticity in pediatric patients has not been established.

Safety and effectiveness in pediatric patients with lower limb spasticity below 2 years of age have not been evaluated.

Safety and effectiveness in pediatric patients with cervical dystonia or upper limb spasticity have not been established.

### **IMPORTANT SAFETY INFORMATION**

#### **Warning: 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 upper limb spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to lower than the maximum recommended total dose.

#### **Contraindications**

Dysport® is contraindicated in patients with known hypersensitivity to any botulinum toxin preparation or to any of the components; or in the presence of infection at the proposed injection site(s); or in patients known to be allergic to cow's milk protein. Hypersensitivity reactions including anaphylaxis have been reported.

#### **Warnings and Precautions**

##### **Lack of interchangeability between botulinum toxin products**

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.

##### **Dysphagia and Breathing Difficulties**

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 side effects occur, additional respiratory muscles may be involved (see Boxed Warning). 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. 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.

### **Pre-existing Neuromuscular Disorders**

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (eg, 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 effects including severe dysphagia and respiratory compromise from typical doses of Dysport®.

### **Human Albumin and Transmission of Viral Diseases**

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

### **Intradermal Immune reaction**

The possibility of an immune reaction when injected intradermally is unknown. The safety of Dysport® for the treatment of hyperhidrosis has not been established. Dysport® is approved only for intramuscular injection.

### **Adverse reactions**

Most common adverse reactions ( $\geq 2\%$  and greater than placebo in either Dysport® group) in adults with upper limb spasticity for Dysport® 500 Units, Dysport® 1000 Units, and Placebo, respectively, were: nasopharyngitis (4%, 1%, 1%), urinary tract infection (3%, 1%, 2%), muscular weakness (2%, 4%, 1%), musculoskeletal pain (3%, 2%, 2%), dizziness (3%, 1%, 1%), fall (2%, 3%, 2%), and depression (2%, 3%, 1%).

Most common adverse reactions ( $\geq 5\%$  and greater than placebo in either Dysport® group) in adults with lower limb spasticity for Dysport® 1000 Units, Dysport® 1500 Units, and Placebo, respectively, were: falls (9%, 6%, 3%), muscular weakness (2%, 7%, 3%), pain in extremity (6%, 6%, 2%). Muscular weakness was reported more frequently in women (10%) treated with 1500 units of Dysport compared to men (5%).

Most common adverse reactions ( $\geq 5\%$  and greater than placebo) in adults with cervical dystonia for Dysport® 500 Units and Placebo, respectively, were: muscular weakness (16%, 4%), dysphagia (15%, 4%), dry mouth (13%, 7%), injection site discomfort (13%, 8%), fatigue (12%, 10%), headache (11%, 9%), musculoskeletal pain (7%, 3%), dysphonia (6%, 2%), injection site pain (5%, 4%), and eye disorders (7%, 2%).

Most common adverse reactions ( $\geq 10\%$  in any group and greater than placebo) in pediatric patients with lower limb spasticity for Dysport® 10 Units/kg, 15 Units/kg, 20 Units/kg, or 30 Units/kg; and Placebo, respectively, were: upper respiratory tract infection (9%, 20%, 5%, 10%, 13%), nasopharyngitis (9%, 12%, 16%, 10%, 5%), influenza (0%, 10%, 14%, 3%, 8%), pharyngitis (5%, 0%, 11%, 3%, 8%), cough (7%, 6%, 14%, 10%, 6%), and pyrexia (7%, 12%, 8%, 7%, 5%).

### **Drug interactions**



Co-administration of Dysport® and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of botulinum toxin may be potentiated. Use of anticholinergic drugs after administration of Dysport® may potentiate systemic anticholinergic effects such as blurred vision. The effect of administering different botulinum neurotoxins at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by another administration of botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of Dysport®.

### **Use in Pregnancy**

Based on animal data Dysport® may cause fetal harm. There are no adequate and well-controlled studies in pregnant women. Dysport® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### **Pediatric Use**

Based on animal data Dysport® may cause atrophy of injected and adjacent muscles; decreased bone growth, length, and mineral content; delayed sexual maturation; and decreased fertility.

### **Geriatric Use**

In general, elderly patients should be observed to evaluate their tolerability of Dysport®, due to the greater frequency of concomitant disease and other drug therapy. Subjects aged 65 years and over who were treated with DYSPOORT® for lower limb spasticity reported a greater percentage of fall and asthenia as compared to those younger (10% versus 6% and 4% versus 2%, respectively).

To report SUSPECTED ADVERSE REACTIONS or product complaints in the United States, contact Ipsen at 1-855-463-5127. You may also report SUSPECTED ADVERSE REACTIONS to the FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Please see Dysport® [Full Prescribing Information](#) including **Boxed Warning** and [Medication Guide](#) for the United States.

### **About Ipsen in North America**

Ipsen Biopharmaceuticals, Inc. is the US affiliate of Ipsen, a global specialty-driven pharmaceutical group. The US head office is located in Basking Ridge, New Jersey. Ipsen Biopharmaceuticals Canada, Inc. is an integrated business unit within North America and has its head office located in Mississauga, Ontario. Ipsen Bioscience, Inc., the Ipsen US research and development center focused on peptide research in oncology and endocrinology, is located in Cambridge, Massachusetts. At Ipsen Bioscience, we focus on creating a highly cooperative and passionate R&D organization through partnerships, innovation, and continuous learning to effectively deliver new treatments for patients. At Ipsen, we focus our resources, investments, and energy on discovering, developing, and commercializing new therapeutic options for oncologic, neurologic, and endocrine diseases. For more information on Ipsen in North America, please visit [www.ipsenus.com](http://www.ipsenus.com) or [www.ipsen.ca](http://www.ipsen.ca).



## **About Ipsen**

Ipsen is a global specialty-driven pharmaceutical group with total sales close to €1.6 billion in 2016. Ipsen sells more than 20 drugs in more than 115 countries, with a direct commercial presence in more than 30 countries. Ipsen's ambition is to become a leader in specialty healthcare solutions for targeted debilitating diseases. Its fields of expertise cover oncology, neurosciences and endocrinology (adult & pediatric). Ipsen's commitment to oncology is exemplified through its growing portfolio of key therapies improving the care of patients suffering from prostate cancer, neuro-endocrine tumors, renal cell carcinoma and pancreatic cancer. Ipsen also has a significant presence in primary care. Moreover, the Group has an active policy of partnerships. Ipsen's R&D is focused on its innovative and differentiated technological platforms, peptides and toxins, located in the heart of the leading biotechnological and life sciences hubs (Les Ulis/Paris-Saclay, France; Slough/Oxford, UK; Cambridge, US). In 2016, R&D expenditures exceeded €200 million. The Group has more than 4,900 employees worldwide. Ipsen's shares are traded on segment A of Euronext Paris (stock code: IPN, ISIN code: FR0010259150) and are eligible to the "Service de Règlement Différé" ("SRD"). The Group is part of the SBF 120 index. Ipsen has implemented a Sponsored Level I American Depositary Receipt (ADR) program, which trades on the over-the-counter market in the United States under the symbol IPSEY. For more information on Ipsen, visit [www.ipсен.com](http://www.ipсен.com).

## **Ipsen Forward Looking Statement**

The forward-looking statements, objectives and targets contained herein are based on the Group's management strategy, current views and assumptions. Such statements involve known and unknown risks and uncertainties that may cause actual results, performance or events to differ materially from those anticipated herein. All of the above risks could affect the Group's future ability to achieve its financial targets, which were set assuming reasonable macroeconomic conditions based on the information available today. Use of the words "believes," "anticipates" and "expects" and similar expressions are intended to identify forward-looking statements, including the Group's expectations regarding future events, including regulatory filings and determinations. Moreover, the targets described in this document were prepared without taking into account external growth assumptions and potential future acquisitions, which may alter these parameters. These objectives are based on data and assumptions regarded as reasonable by the Group. These targets depend on conditions or facts likely to happen in the future, and not exclusively on historical data. Actual results may depart significantly from these targets given the occurrence of certain risks and uncertainties, notably the fact that a promising product in early development phase or clinical trial may end up never being launched on the market or reaching its commercial targets, notably for regulatory or competition reasons. The Group must face or might face competition from generic products that might translate into a loss of market share. Furthermore, the Research and Development process involves several stages each of which involves the substantial risk that the Group may fail to achieve its objectives and be forced to abandon its efforts with regards to a product in which it has invested significant sums. Therefore, the Group cannot be certain that favourable results obtained during pre-clinical trials will be confirmed subsequently during clinical trials, or that the results of clinical trials will be sufficient to demonstrate the safe and effective nature of the product concerned. There can be no guarantees a product will receive the necessary regulatory approvals or that the product will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements. Other risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health

care legislation; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the Group's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the Group's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions. The Group also depends on third parties to develop and market some of its products which could potentially generate substantial royalties; these partners could behave in such ways which could cause damage to the Group's activities and financial results. The Group cannot be certain that its partners will fulfil their obligations. It might be unable to obtain any benefit from those agreements. A default by any of the Group's partners could generate lower revenues than expected. Such situations could have a negative impact on the Group's business, financial position or performance. The Group expressly disclaims any obligation or undertaking to update or revise any forward looking statements, targets or estimates contained in this press release to reflect any change in events, conditions, assumptions or circumstances on which any such statements are based, unless so required by applicable law. The Group's business is subject to the risk factors outlined in its registration documents filed with the French Autorité des Marchés Financiers. The risks and uncertainties set out are not exhaustive and the reader is advised to refer to the Group's 2016 Registration Document available on its website ([www.ipsen.com](http://www.ipsen.com)).

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