

Ipsen Announces Efficacy and Safety Data for Dysport® (abobotulinumtoxinA) Across Multiple Therapeutic Uses at the 2018 Annual Meeting of the American Academy of Neurology

Analyses of Pooled Data of Dysport® for the Treatment of Pediatric Lower Limb Spasticity Indicate a Consistent Safety Profile

BASKING RIDGE, N.J., April 23, 2018 – Ipsen Biopharmaceuticals, Inc., an affiliate of Ipsen (Euronext: IPN; ADR: IPSEY) (Ipsen), will present Dysport® (abobotulinumtoxinA) data across multiple therapeutic uses at the annual meeting of the American Academy of Neurology (AAN) being held April 21-27, 2018 in Los Angeles. The presentations include a safety analysis of pooled data of Dysport® for pediatric lower limb (PLL) spasticity in patients two to 17 years old, including nearly 200 children aged two to five years. Evaluation of Physician’s Global Assessment (PGA) response to repeated Dysport® injections in adult lower limb (ALL) spasticity will be presented. Additionally, data on the persistence of therapeutic benefits after a single injection cycle of Dysport® on the clinical symptoms of cervical dystonia (CD) in adults will also be shared. These are three of seven Dysport® posters being presented at the meeting.

“The analyses presented at AAN reinforce the efficacy and safety profile for Dysport® in multiple therapeutic uses, doses and injection cycles,” said **Francois LaFleur, Vice President Global Medical Affairs, North & South America, Ipsen**. “The results provide important confirmatory information for physicians when determining the appropriate treatment option for their adult and pediatric patients.”

A pooled analysis of safety data from four placebo-controlled clinical trials in 386 children aged two to 17 years old with lower limb spasticity due to cerebral palsy was conducted. Results showed that the safety profile of Dysport® across age groups is consistent. Most adverse events (AEs) reported were related to common childhood illnesses. The preschool group included 299 children aged two to five years (Dysport®=195; placebo=104), the elementary school group included 134 children aged six to nine years (Dysport®=87; placebo=47) and the middle/high school group included 43 children aged 10+ years (Dysport®=30; placebo=13). Individual adverse event data for each study were pooled to form one database. Rates of treatment emergent adverse events (TEAEs) (Dysport® vs. placebo) were: preschool (60.5 percent vs. 52.9 percent), elementary school (58.6 percent vs. 36.2 percent), middle/high school (40.0 percent vs. 46.2 percent). Rates of TEAEs considered related to Dysport® treatment were low across all age groups: preschool (14.9 percent vs. 8.7 percent), elementary school (11.5 percent vs. 2.1 percent), middle/high school (6.7 percent vs. 15.4 percent). The only serious TEAE considered to be treatment related occurred in a middle/high school aged child (moderate muscle pain and weakness in the 30 U/kg group), which led to the only premature study withdrawal (Abstract #323).

“As the only FDA-approved treatment for lower limb spasticity in pediatric patients two years of age and older, these data reinforce the importance of having FDA-recommended dose ranges where the safety and tolerability of Dysport® has been characterized,” **LaFleur** added. “A key point about this pooled analysis is the assessment of a large group of pediatric patients aged two to five, a sensitive age range when deciding upon a course of treatment.”

A Phase 3, randomized, placebo-controlled study was conducted to evaluate the PGA of treatment response after repeated injections of Dysport[®] in traumatic brain injury or stroke patients with ALL spasticity. This study had a double-blind, single-cycle phase (n = 388) and an open-label (OL) multicycle extension. The PGA, assessed on a nine-point ordinal scale from -4 (markedly worse) to +4 (markedly improved), is a commonly used scale for evaluating treatment response in clinical trials with botulinum toxins. Data showed that the mean PGA score at week 4 increased across treatment cycles, with both Dysport[®] 1000U and 1500U (+1.0 in the double-blind phase [double-blind placebo group: +0.7] to +1.8 and +1.9 in cycle 4 of the OL extension for 1000U and 1500U, respectively). The proportion of responders (PGA score of \geq +1) treated with Dysport[®] 1000U and 1500U increased from 58.0 percent and 62.5 percent, respectively, at week 4 of the double-blind phase (double-blind placebo group: 49.2 percent) to 86.4 percent and 96.1 percent, respectively, at week 4 of cycle 4. The latter results confirmed that the maximum clinical benefit (as measured by the PGA) was obtained after repeat dosing of Dysport[®] in the lower extremity using the most effective dosing regimen in adult post-stroke or traumatic brain injury patients (Abstract #011).

The third presentation highlights results from a meta-analysis that evaluated the impact of one injection cycle of Dysport[®] on the clinical characteristics of CD and persistence of therapeutic benefits. Two observational international studies and one registry (from the United States) were selected for this analysis (total n=1,091). The majority (84.4 percent) had received previous botulinum toxin treatment. Assessments were performed at baseline/first injection and at the end of the cycle/next injection. Clinical efficacy assessments included the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and Tsui tremor scores. Of evaluated patients, 73.9 percent had an injection interval of 12-16 weeks between visit one and visit two, and 23.1 percent had an interval of more than 16 weeks. Additionally, persistent improvements between injection visits were noted in TWSTRS total, severity, disability and pain scores, and the proportion of patients categorized as having severe tremor associated with CD decreased between injections. Results confirmed that the clinical symptoms of CD may not fully return to baseline by 12 weeks following a single injection cycle of Dysport[®] (Abstract #047).

Dysport[®] (abobotulinumtoxinA) and all botulinum toxin products have a Boxed Warning in the US 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 scroll below for additional Important Safety Information.**

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.¹ 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 (MS), stroke and brain or head trauma.¹ 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.^{2,3}

Lower limb spasticity commonly involves spasticity in the gastrocnemius and soleus muscle complex located in the calf.^{4,5} These calf muscles, during walking, work to raise the heel from the ground.⁴ Symptoms of spasticity may include increased muscle tone, rapid muscle contractions, exaggerated deep tendon reflexes, and/or muscle spasms.¹ The degree of spasticity can vary from mild muscle stiffness to severe, painful and uncontrollable muscle spasms.¹

About Cervical Dystonia

Cervical dystonia (CD), also known as spasmodic torticollis, is a movement disorder in which involuntary muscular contractions occur primarily in the neck muscles.⁶ These contractions can cause the head to turn to one side or be pulled forward or backward.⁷

CD is a relatively uncommon condition, affecting 57 to 280 people per million.⁸ The disease can occur at any age, although symptoms generally appear in middle age.⁷ It often begins slowly and usually reaches a plateau over a few months or years.⁷

CD can be particularly painful due to degeneration of the spine, irritation of nerve roots or frequent headaches.⁹ In most cases the cause is unknown and no cure exists.⁸

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.

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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

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

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 or 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. 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 (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 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.

Most Common Adverse Reactions

Adults with upper limb spasticity ($\geq 2\%$ and greater than placebo): nasopharyngitis, urinary tract infection, muscular weakness, musculoskeletal pain, dizziness, fall, and depression.

Adults with lower limb spasticity ($\geq 5\%$ and greater than placebo): falls, muscular weakness, and pain in extremity.

Adults with cervical dystonia ($\geq 5\%$ and greater than placebo): muscular weakness, dysphagia, dry mouth, injection site discomfort, fatigue, headache, musculoskeletal pain, dysphonia, injection site pain, and eye disorders.

Pediatric patients with lower limb spasticity ($\geq 10\%$ and greater than placebo): upper respiratory tract infection, nasopharyngitis, influenza, pharyngitis, cough, and pyrexia.

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 Dysport for lower limb spasticity reported a greater percentage of fall and asthenia as compared to those younger (10% vs. 6% and 4% vs. 2%, respectively).

To report SUSPECTED ADVERSE REACTIONS or product complaints, 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.

Please see [Full Prescribing Information](#), including **Boxed Warning** and [Medication Guide](#).

About Ipsen in North America

Ipsen Biopharmaceuticals, Inc. is a U.S. affiliate of Ipsen (Euronext: IPN; ADR: IPSEY), a global specialty-driven biopharmaceutical group focused on innovation and specialty care. The U.S. head office is located in Basking Ridge, New Jersey, and its Canadian office, Ipsen Biopharmaceuticals Canada, Inc., an integrated business unit within North America, is located in Mississauga, Ontario. Additional research and development and manufacturing sites are located in Cambridge, Massachusetts, as part of Ipsen Bioscience, Inc., the Ipsen U.S. research and development center, which is focused on the discovery of potentially highly differentiated and competitive products in Oncology, Neurosciences and Rare Diseases. Ipsen North America employs more than 400 people and is dedicated to providing hope for the patients whose lives are challenged by difficult-to-treat diseases. At Ipsen, we focus our resources, investments and energy on discovering, developing and commercializing new therapeutic options for oncologic, neurologic and rare diseases. For more information on Ipsen in North America, please visit www.ipsenus.com or www.ipsen.ca.

About Ipsen

Ipsen is a global specialty-driven biopharmaceutical group focused on innovation and specialty care. The group develops and commercializes innovative medicines in three key therapeutic areas - Oncology, Neurosciences and Rare Diseases. Its commitment to oncology is exemplified through its growing portfolio of key therapies for prostate cancer, neuroendocrine tumors, renal cell carcinoma and pancreatic cancer. Ipsen also has a well-established Consumer Healthcare business. With total sales over €1.9 billion in 2017, Ipsen sells more than 20 drugs in over 115 countries, with a direct commercial presence in more than 30 countries. Ipsen's R&D is focused on its innovative and differentiated technological platforms located in the heart of the leading biotechnological and life sciences hubs (Paris-Saclay, France; Oxford, UK; Cambridge, US). The Group has about 5,400 employees worldwide. Ipsen is listed in Paris

(Euronext: IPN) and in the United States through a Sponsored Level I American Depositary Receipt program (ADR: IPSEY). For more information on Ipsen, visit www.ipсен.com.

Forward Looking Statements

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 favorable 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 fulfill 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.

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Dysport® (abobotulinumtoxinA) for injection, for intramuscular use 300- and 500-Unit vials.

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