

Ipsen announces publication in *Neurology* of results of two studies demonstrating the efficacy and safety of Dysport® (abobotulinumtoxinA) in adult patients with lower limb spasticity

Results led to regulatory approval of Dysport® for the treatment of lower limb spasticity in adults in the U.S. in 2017 and in some European countries in 2016

Paris (France), 29 November 2017 – Ipsen (Euronext: IPN; ADR: IPSEY) today announced that detailed results from a Phase III randomized, double-blind, placebo-controlled study (NCT01249404) and its open-label extension study (NCT01251367) have been published in the current issue of *Neurology*¹, demonstrating the efficacy and safety of Dysport® (abobotulinumtoxinA) in adult patients with lower limb spasticity following a stroke or traumatic brain injury.

The international phase III registration study led to the U.S. Food and Drug Administration (FDA) expanded approval of Dysport® for injection for the treatment of spasticity in adults, based on its supplemental Biologics License Application (sBLA) in lower limb spasticity, on June 16, 2017. This same study has been the basis for marketing authorization in other key markets, including the UK and Germany, in late 2016, and regulatory procedures are still ongoing in other countries.

These two studies¹ demonstrated the efficacy and safety of Dysport® in adults with hemiparesis who experienced lower limb spasticity. The results showed that, in this population, single Dysport® administration reduced muscle tone, while repeated administration over a year was well-tolerated and improved both walking speed and likelihood of achieving community ambulation. In the U.S., Dysport® has a boxed warning in its product label regarding distant spread of toxin effect. See below for important safety information.

Alexandre Lebeaut, Executive Vice President R&D and Chief Scientific Officer, Ipsen stated: *“The results of the Phase III studies (double-blind and open-label) published this month in Neurology underline the significant clinical benefit for adult patients with lower limb spasticity who received repeated injections of Dysport®. Similar to what we observed in adults with upper limb spasticity, many of these patients experienced a duration of response between 12-16 weeks, and some patients ever experienced a longer duration of response up to 20 weeks. I would like to thank all the clinicians, patients and their families who participated in these worldwide studies.”*



Professor Jean-Michel Gracies, Neurorehabilitation, Neurology & Neurophysiology, Chairman of the Department of Neurorehabilitation, Groupe Hospitalier Albert CHENEVIER - Henri MONDOR (Créteil, France) stated: *“This publication in Neurology demonstrates both the short-term efficacy of Dysport® in improving muscle tone in adult patients with lower limb spasticity and also the long-term improvements with repeated treatment cycles. Dysport® was shown to improve outcomes for these patients, including substantial improvements in walking speed.”*

About the Phase III Study Conducted in Adults with Lower Limb Spasticity Treated with Dysport®

The Phase III, multi-center, prospective, double-blind, randomized placebo-controlled study (NCT01249404¹), 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 (Modified Ashworth Scale [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 (GSC) 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.²

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, 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 majority of patients in the study experienced a response duration of 12-16 weeks, while some 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 ($\geq 5\%$ and greater than placebo) in adults with lower limb spasticity were: falls, muscular weakness, and pain in extremity.



About the Open-Label Phase III Study Conducted in Adults with Lower Limb Spasticity Treated with Dysport®

The Phase III study (NCT01251367) was a multi-center, prospective, open-label, multiple-cycle extension of the double-blind study. The primary endpoint of the open-label study was long-term safety, with long-term efficacy as a secondary endpoint.

During the first treatment cycle of the open-label study, all participants received Dysport® 1500 U except for those participants who experienced treatment-emergent adverse events (TEAEs) during the double-blind phase, who received Dysport® 1000 U. For subsequent cycles, Dysport® 1000 U or 1500 U was administered based on the investigator's judgment.

Throughout the open-label study, the Dysport® tolerability profile remained consistent. The incidence of TEAEs decreased across repeated treatment cycles with both doses of Dysport®, with most TEAEs being mild to moderate. Overall, 19 participants withdrew due to TEAEs, 11 of which were considered to be treatment-related. Across all treatment cycles, 11 percent of participants experienced serious adverse events (SAEs). There were 2 deaths that both occurred in the Dysport® 1500 U group, 1 suicide and 1 respiratory failure, neither of which was considered to be treatment-related.

Dysport® was shown to be efficacious across repeated treatment cycles. Muscle tone improvements observed in the double-blind study remained stable from Cycle 2 onwards, with -0.9 change from baseline in MAS GSC and -1.1 in MAS soleus (Dysport® doses combined). Physician global assessment (PGA) scores continued to improve with repeat treatment, reaching 1.9 by Week 4 of Cycle 4. In addition, participants experienced improvements in active function as assessed by the 10m comfortable barefoot walking speed test. Walking speed increased across repeated Dysport® treatment cycles, reaching an improvement from double-blind study baseline of 25.35 percent (95 percent confidence interval 17.48–33.21) at Week 4 of Cycle 4.

While the majority of patients in each open-label cycle were re-treated at Week 12, many had longer-lasting results and were treated at Week 16 and beyond.

About Dysport®

Dysport® is an injectable form of a botulinum neurotoxin type A (BoNT-A) product, which is a substance derived from Clostridium bacteria producing BoNT-A that inhibits the effective transmission of nerve impulses and thereby reduces muscular contractions. It is supplied as a lyophilized powder. As of 31 December 2016, Dysport® had marketing authorization in more than 80 countries.

INDICATIONS AND IMPORTANT SAFETY INFORMATION for the United States

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 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.

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

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.³ 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.^{4,5}

Lower limb spasticity commonly involves spasticity in the gastrocnemius and soleus muscle complex located in the calf.^{6,7} These calf muscles, during walking, work to raise the heel from the ground.⁶ 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.³

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 close to €1.6 billion in 2016, 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, and centers located in the heart of the leading biotechnological and life sciences hubs (Paris-Saclay, France; Oxford, UK; Cambridge, US). The Group has about 5,100 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.ipsen.com.

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 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 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).

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