

Dysport® (clostridium botulinum type A toxin-haemagglutinin complex) now approved in the UK for symptomatic treatment of upper limb spasticity in children with cerebral palsy

- *Making it the first and only botulinum toxin in the UK to be approved for the treatment of pediatric spasticity in both upper and lower limbs*
- *The first botulinum toxin approval in pediatric upper limb spasticity in Europe in over a decade*

PARIS, France, 06 January 2020 — Ipsen (Euronext: IPN; ADR: IPSEY) today announced that the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) has granted a licence update for Dysport® for the symptomatic treatment of focal spasticity of upper limbs in pediatric cerebral palsy patients, two years of age and older.

Spasticity in children is most commonly associated with cerebral palsy (CP).^{1,2} Approximately 17 million people worldwide are affected by cerebral palsy, with an estimated 1 in 400 babies born with cerebral palsy in the UK, 75-91% of whom will have a specific type known as spastic cerebral palsy.^{1,2} For these children, spasticity affects muscle tone, movement, and motor skills, hindering their ability to move in a coordinated and purposeful way, which can consequently impact on their ability to participate in everyday activities.³

“Therapeutic options such as botulinum toxin type A are an important part of the multidisciplinary approach for treating spasticity,” said Alison Smith, Consultant Pediatric Neuro-physiotherapist, NPP Neuro Group, UK. “They work by interrupting the muscle contraction and thereby reducing stiffness related to spasticity with the aim of helping children with cerebral palsy to not only improve physical functioning but also achieve their goals which can improve their mental and emotional wellbeing. Having a therapeutic option approved for both upper and lower limb indications creates a real benefit for the patient as it allows a holistic treatment approach for any patients with multi-focal spasticity.”

This approval was based on the Phase III study demonstrating that Dysport® reduced spasticity symptoms in children aged two years and older being treated for upper limb spasticity due to cerebral palsy, as measured by the Modified Ashworth Scale (MAS), which is the standard scale for assessing muscle resistance associated with spasticity.⁴ The safety profile was consistent with that seen in the approved indications for pediatric cerebral palsy lower limb spasticity after repeated injections and no new safety concerns were identified.⁵

Asad Mohsin Ali, UK & Ireland General Manager, Ipsen said “Today’s approval is an important advancement for children in the UK living with cerebral palsy, who can now benefit from long-lasting symptom relief between their botulinum toxin A injections. As a father myself, I am proud that Ipsen is the first company to have obtained this approval that may help children live as normal a life as possible.”

Effective treatment of spasticity requires a highly specialized, multidisciplinary approach including physiotherapy and occupational therapy to reduce overactivity and the risk of permanent muscle shortening, thus promoting functional activity and helping to allow the child to participate in their daily activities.⁶

About Pediatric Cerebral Palsy Spasticity

Spasticity is abnormal and involuntary muscle stiffness, or overactivity (contractions) in a group of muscles⁷, which causes them to have increased tone, leading to stiffness or tightness.⁸ Cerebral palsy (CP) is the leading cause of childhood disability affecting function and development, and the most frequent cause of spasticity in children.³ Approximately 17 million people worldwide are affected by cerebral palsy, with an estimated 1 in 400 babies born in the UK have a type of CP, approximately 90% of whom will develop spastic cerebral palsy.^{1,2}

Upper limb spasticity in children is a condition that causes muscle spasms in the elbow, wrist, and finger muscles.⁹ Lower limb spasticity is a condition that causes increased muscle stiffness in the calf, which, can prevent the ankle from flexing as needed and causes the foot to be pointed down and in.¹⁰ Upper limb is the most common form of spasticity and is a significant source of disability particularly in children where impaired muscle growth can lead to abnormal posturing and deformities causing pain and difficulties performing daily tasks such as washing.^{11,12}

About the Phase III Pivotal Study

Dysport[®] was evaluated in a Phase III, randomized, double-blind, low-dose controlled, multicenter study that included a total of 210 children treated, aged two to 17 years, for upper limb spasticity.¹³ Patients with a MAS of Grade 2 or greater at the primary targeted muscle groups (PTMG) were enrolled and received doses of Dysport[®] at 8 Units/kg (n=70), 16 Units/kg (n=70) or 2 Units/kg (n=70) injected into the PTMG (elbow flexors: brachialis and brachioradialis or wrist flexors: flexor carpi radialis, and flexor carpi ulnaris).¹³ After the initial treatment, up to three further treatments of Dysport[®] could be administered at planned doses of either 8 Units/kg or 16 Units/kg, or titrated up or down according to investigator judgement.¹³ Primary endpoint was mean change in MAS score from baseline to Treatment 1 at week 6 in Primary Targeted Muscle Group (elbow flexors or wrist flexors); secondary endpoints were mean Physician Global Assessment (PGA) score and Goal Attainment Scale (GAS) score at week 6. Spasticity improvements were also assessed using the Tardieu scale as a tertiary endpoint. Also included were safety assessments.¹³

Dysport[®] showed statistically significant improvements from baseline in MAS in the PTMG at Week 6, the primary endpoint, with doses of 8 Units/kg and 16 Units/kg compared to low dose Dysport[®] (2 Units/kg) (-2.0, -2.3 and -1.6, respectively).¹⁴ A total of 208 patients were included in this assessment as part of the modified intent to treat (mITT) population.¹⁴ Dysport[®] (16 Units/kg) received a mean +2.0 Physician Global Assessment (PGA) score, though there was no statistically significant difference in mean PGA (2.0, 2.0 and 1.8, respectively) or mean Goal Attainment Scale (GAS) (52.6, 52.6 and 52.1, respectively) between groups.¹⁴ In the upper limb study, a majority of patients were retreated between 16-28 weeks; however, some patients had a longer duration of response (i.e., 34 weeks or more).¹⁴ The safety profile was consistent with that seen in the approved indications for pediatric cerebral palsy lower limb spasticity after repeated injections and no new safety concerns were identified.⁵

About Dysport[®]

Dysport[®] is an injectable form of a botulinum neurotoxin type A product, which is a substance derived from Clostridium bacteria producing botulinum toxin type A (BoNT-A) that inhibits the effective transmission of nerve impulses and thereby reduces muscular contractions.¹⁵ It is supplied as a lyophilized powder. As of 31 December 2018, Dysport[®] had marketing authorization in more than 85 countries for therapeutic treatment indications and more than 30 years of clinical experience. Dysport[®] was first approved in the U.K. in 1990 for the treatment of blepharospasm and hemifacial spasm.¹⁶

Dysport[®] is indicated for symptomatic treatment of focal spasticity of upper limbs in adults, lower limbs in adults affecting the ankle joint due to stroke or traumatic brain injury (TBI) and dynamic equinus foot deformity in ambulant pediatric cerebral palsy patients, two years of age or older. Dysport[®] is also indicated in adults for symptomatic treatment of spasmodic torticollis, blepharospasm, hemifacial spasm and severe primary hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics.

Dysport® should only be administered by appropriately trained physicians. For the treatment of focal spasticity, Dysport® can also be administered by healthcare professionals having received appropriate training and qualification in accordance with national guidelines (e.g. Royal College of Physicians).²

Ipsen co-developed Dysport® in partnership with the UK Government bodies, specifically the Center for Applied Microbiology and Research¹⁴ and provides continued value through a quarterly royalty to Public Health England which totaled more than £30m in 2018.¹⁷

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, Neuroscience 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 €2.2 billion in 2018, 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 5,700 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 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 2018 Registration Document available on its website (www.ipсен.com).

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