CHMP recommends Approval of Xadago™ (safinamide) to treat Parkinson´s disease in the EU

- First New Chemical Entity (NCE) in 10 years to receive a positive opinion from CHMP for the treatment of Parkinson's disease (PD) patients
- Positive Opinion for Use of Safinamide as Add-on to L-dopa alone or in combination with other Parkinson's disease medications in mid-late stage PD patients with motor fluctuations
- Decision based on the results of two international Phase III placebo-controlled studies in over 1,100 patients
- Safinamide's profile is differentiated from "standard of care" demonstrating sustained efficacy in the long term (more than two years)

Milan, Italy, December 19, 2014 – Newron Pharmaceuticals S.p.A. ("Newron"), a research and development company focused on novel CNS and pain therapies, and its partner Zambon S.p.A., an international pharmaceutical company strongly committed to the CNS therapeutic area, announced today that the EU Committee for Medicinal Products for Human Use (CHMP) recommended that the European Commission approve the use of Xadago™ (safinamide) as add-on to L-dopa alone or in combination with dopamine agonists, entacapone, amantadine, and/or anticholinergics, for the treatment of patients with mid-late stage Parkinson's disease experiencing motor fluctuations despite being stabilized on 'Standard of Care'.

C. Warren Olanow, M.D., FRCPC, Henry P. and Georgette Goldschmidt Professor and Chairman Emeritus of the Department of Neurology and Professor of Neuroscience at the Mount Sinai School of Medicine, stated: "Safinamide is the first NCE to be approved for the treatment of Parkinson's disease in the past 10 years. In a two year double blind study, the product demonstrated rapid onset of efficacy (within two weeks) and benefit with respect to improvements in 'ON and OFF Time' without an increase in dyskinesia. This was maintained for the two year duration of the trial when used as an add-on treatment to PD patients with L-dopa-induced motor fluctuations, compared with 'Standard of Care'. No other agent has demonstrated this duration of benefit in a double blind trial. Safinamide's effects are dependent upon pharmacological mechanisms that are not shared with other PD drugs. These effects include its dual mechanism of highly selective, reversible inhibition of MAO-B, and state and use-dependent blockade of sodium channels that inhibit glutamate release, implicated in causing dyskinesia. Preclinical experiments and data from a large number of dyskinetic patients enrolled in a placebo controlled clinical study indicate that safinamide also has the potential to improve L-dopa induced dyskinesia in PD patients."

Fabrizio Stocchi, M.D., Professor of Neurology, Director of the Parkinson's Disease and Movement Disorders Research Centre, and Institute for Research and Medical Care IRCCS San Raffaele, Rome, who has been involved with safinamide trials from the be-

ginning, said: “The benefits of safinamide were demonstrated as adjunctive treatment for fluctuating patients on top of L-dopa alone or in combination with other PD medications. Safinamide demonstrated significantly improved motor fluctuations, Parkinsonism, Quality of Life and Activities of Daily Living without any increase in ‘ON Time with troublesome dyskinesia’. My experience in treating PD patients with safinamide in Rome over the last 10 years, as well as my review of all the data indicate that safinamide is extremely well tolerated even over long periods of time. Safinamide does not require any specific medical monitoring, dietary restrictions, or particular precautions because the risk of drug interactions is very low”.

Ravi Anand, M.D., Newron’s CMO, said, “The CHMP decision on safinamide is a great result for PD patients and physicians, providing them with a therapeutic alternative that is an improvement over “standard of care” in patients with mid-late stage Parkinson’s disease patients on L-dopa, who constitute a major proportion (over 75%) of those that are experiencing this progressive debilitating disease. Safinamide’s unique profile of rapid onset and long lasting efficacy, significant even at two years, in a randomized placebo-controlled trial, has not been demonstrated with any other PD medication. In addition, safinamide improved patient and care giver rated Quality of Life measures, including PDQ39 and EQ-5D, as well as depressed mood. We thank the CHMP and EMA staff for their scientific advice during the development of safinamide and performing a timely review of the MAA”.

Maurizio Castorina, CEO of Zambon, said, “We are very excited by the decision of the CHMP that recognizes the therapeutic benefits of Xadago™. We now eagerly await the EU Marketing Authorization from the European Commission, so this product can be launched and its benefits made available to Parkinson’s disease patients starting in the first half of 2015. Zambon will make its best effort for the expeditious availability of Xadago™ and its success in the marketplace”.

The CHMP’s positive opinion on Xadago™ will now be reviewed by the European Commission, which has the authority to approve medicines for the European Union. The final decision will be applicable to all 28 European Union member countries, as well as Iceland, Liechtenstein and Norway.

Conference call

Newron management will host a conference call on Friday, Dec. 19, 2:00 pm CET, which can be accessed via the following dial-in numbers:

+41 (0)58 310 50 00 (Europe)
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Safinamide Development Program
The EU filing was based on results of a comprehensive development program comprising over 300 preclinical studies and 37 clinical studies performed in over 30 countries worldwide, with over 3,000 subjects treated, and safinamide's safety being documented in >1,100 patients for 1 year, >500 patients for 2 years, >220 patients for 3 years, and >160 patients for 4 years.

Safinamide Pivotal L-dopa Studies
The efficacy of safinamide as add-on treatment in mid-late stage PD (LSPD) patients with motor fluctuations, currently receiving L-dopa alone or in combination with other PD medications, was evaluated in two double-blind, placebo-controlled studies: SETTLE (Study 27919; 50-100 mg/day; 24 weeks; N=549), and Study 016/018 (50 and 100 mg/day; 2 year double-blind, placebo-controlled study; N=669).

The results of analyses (mITT, 'On-treatment' population; MMRM) for Study 016/018 and the SETTLE study indicate a consistent pattern of benefit for motor fluctuations with statistically significant improvements in the Primary efficacy measure, daily ON Time (ON Time without troublesome dyskinesia), and key secondary measure of OFF Time as recorded by the patients in the 18-hr diary. Statistically significant efficacy was also noted for secondary measures including motor symptoms (UPDRS III), Quality of Life (as indicated by changes in the patients/care-giver rated PDQ39, EQ-5D), depressive symptoms, as measured by the GRID-HAMD scale, global change from baseline (CGI-C) assessed by the clinician, and activities of daily living (UPDRS II) assessed by the patient/caregiver.

In the SETTLE study, statistically significant improvements from baseline to endpoint were observed for safinamide, compared to placebo (LS mean difference), for ON Time (0.9 h, 95% CI [0.6, 1.2], p<0.0001), OFF Time (-1.0 h, 95% CI [-1.3, -0.7], p<0.0001), UPDRS III (-1.82, 95% CI [-3.01, -0.62], p=0.003), UPDRS II, (-0.4, p=0.0564), PDQ-39 (p=0.006) and EQ-5D (p<0.001). The proportion of patients rated as "very much/much" improved on the CGI-C at endpoint was significantly greater for safinamide (24.4%, p<0.0001) compared to placebo (9.5%). Furthermore, additional responder rate analyses demonstrated a spectrum of benefit that was reflected in a greater proportion of safinamide-treated patients, compared to placebo, having clinically important improvement (≥1 hour) in ON Time and OFF Time, along with 30% improvement in UPDRS III (18.1% vs. 8.8%, p=0.0017).

In the initial 6-month treatment period of Study 016/018, statistically significant improvements from baseline to endpoint were observed for the safinamide 50 and 100 mg/day doses, compared to placebo (LS mean difference), for ON Time (50 mg/day: 0.5 h, 95% CI [0.1, 0.9], p=0.0054; 100 mg/day: 0.7 h, 95%CI [0.3, 1.0], p=0.0002), OFF Time (50 mg/day: -0.6 h, 95% CI [-0.9, -0.3], p=0.0002; 100 mg/day: -0.7 h, 95% CI [-1.0, -0.4], p<0.0001), UPDRS III (50 mg/day: -1.6, 95% CI [-3.0, -0.2], p=0.0207; 100 mg/day: -2.3, 95% CI [-3.7, -0.9], p=0.0010) and UPDRS II (50 mg/day: -0.7, 95% CI [-1.3, -0.0], p=0.0367; 100 mg/day: -1.1, 95% CI [-1.7, -0.5], p=0.0007). The proportion of patients

rated as “very much/much” improved on the CGI-C at endpoint was significantly greater for safinamide (50 mg/day: 33.2%, p=0.0017; 100 mg/day: 36.1%, p=0.0002) compared to placebo (19.8%). Furthermore, responder rate analyses showed a greater proportion of safinamide-treated patients, compared to placebo, having clinically important improvement (≥1 hour) in ON Time and OFF Time, along with 30% improvement in UPDRS III (50 mg/day: 24.0%, p=0.0216; 100 mg/day: 25.9%, p=0.0061 vs. Placebo: 15.1%), UPDRS II (ADL), 100mg/day: -1.0, 95% CI [-1.7;-0.3], p=0.0060, and PDQ39 (Total Score) -16.5, 95% CI (-31.9, -1.1), p=0.0360.

The benefits of safinamide were still significant following two years of treatment as assessed in Study 018. Statistically significant improvements from baseline to endpoint were observed for safinamide, compared to placebo (LS mean difference), for ON Time (50 mg/day: 0.6 h, 95%CI [0.1, 1.0], p=0.0110; 100 mg/day: 0.7 h, 95%CI [0.2, 1.1], p=0.0028), OFF Time (50 mg/day: -0.5 h, 95% CI [-0.8, -0.2], p=0.0028; 100 mg/day: -0.6 h, 95% CI [-0.9, -0.3], p=0.0003), UPDRS III (100 mg/day: -2.1, 95% CI [-3.5, -0.6], p=0.0047) and UPDRS II (100 mg/day: -1.1, 95% CI [-1.8, -0.4], p=0.0010), GRID-HAMD (100mg/day: -0.57, 95% CI [-1.13, -0.01], p<0.05), and PDQ39 Total Score (100mg/day: -18.36, 95% CI [-33.75, -2.97], p=0.0195).

In the Pooled Studies 016 and SETTLE, statistically significant improvement was observed with safinamide for ON Time without troublesome dyskinesia (50 mg/day: 0.5 hr, p=0.0010; 100 mg/day: 0.7 hr, p<0.0001) and OFF Time (50 mg/day: -0.6 hr, p<0.0001; 100 mg/day: -0.9 hr, p<0.0001), compared with placebo. Statistically significant improvement was observed for the UPDRS III for both doses compared to placebo (50 mg/day: -1.5, p=0.0052; 100 mg/day: -1.5, p=0.0002). In the responder analysis for Pooled Studies 016/SETTLE, a significantly higher proportion of patients in both safinamide groups (50 mg/day: 54.8%, p=0.0106; 100 mg/day: 56.2%, p<0.0001) compared with placebo (43.1%) showed improvement of ≥ 60 minutes in ON Time, and a significantly greater proportion of patients were rated as “very much/much” improved on the CGI-C (50mg/day: 33.2%, p=0.0002; 100mg/day: 29.6%, p<0.0001) compared with placebo (14.0%).

Studies in patients with early-stage PD
The efficacy of safinamide as add-on treatment to a single dopamine agonist was evaluated in 3 double-blind, placebo-controlled studies: Study 009 (0.5 and 1.0 mg/kg/day [~40 and 80 mg/day, respectively]; 12 weeks, N=100), Study 015/017 (50-100 and 150-200 mg/day; 24 weeks followed by a 52-week double-blind, placebo-controlled extension, N=269) and MOTION (Study 27918; 50 and 100 mg/day; 24 weeks followed by a 78-week double-blind, placebo-controlled extension, N=678).

In these studies, safinamide 50 and 100 mg/day demonstrated statistically significant improvements on the Primary efficacy measure and key selected secondary measures, however, the CHMP concluded that the medical need for additional medication for these early-stage patients, together with the magnitude of the benefit seen with safinamide in this patient group, did not provide compelling grounds for approval for this use in Europe.

About Parkinson's disease

PD is the second most common chronic progressive neurodegenerative disorder in the elderly after Alzheimer's disease, affecting 1-2% of individuals aged ≥ 65 years worldwide. The prevalence of the PD market is expected to grow in the next years due to the increase in the global population and advancements in healthcare that contribute to an aging population at increased risk for Parkinson's disease. The diagnosis of PD is mainly based on observational criteria of muscular rigidity, resting tremor, or postural instability in combination with bradykinesia. As the disease progresses, symptoms become more severe. Early stage patients are more easily managed on L-dopa. L-dopa remains as the most effective treatment for PD, and over 75% of the patients with PD receive L-dopa. However, long term treatment with L-dopa leads to seriously debilitating motor fluctuations, i.e. phases of normal functioning (ON time) and decreased functioning (OFF time). Furthermore, as a result of the use of high doses of L-dopa with increasing severity of the disease, many patients experience involuntary movements known as L-dopa-Induced Dyskinesia (LID). As the disease progresses, more drugs are used as an add-on to what the patient already takes, and the focus is to treat symptoms while managing LID and the OFF time" effects of L-dopa. Most current therapies target the dopaminergic system that is implicated in the pathogenesis of PD, and most current treatments act by increasing dopaminergic transmission that leads to amelioration of motor symptoms. There is a growing belief that targeting non-dopaminergic systems may lead to improvements in PD symptoms such as dyskinesia that are not improved by current dopaminergic therapies.

About Newron Pharmaceuticals

Newron (SIX: NWRN) is a biopharmaceutical company focused on the development of novel therapies for patients with diseases of the Central Nervous System (CNS) and pain. The Company is headquartered in Bresso near Milan, Italy. Following the submission of the Marketing Authorization Application (MAA) for safinamide for the treatment of Parkinson's disease to the European Medicines Agency (EMA) in December 2013, to Swissmedic in March, 2014 as well as the New Drug Application NDA to the US FDA, Newron is working towards global approval of the compound, together with its partners. Zambon Group has the rights to commercialize safinamide globally, excluding Japan and other key Asian territories where Meiji Seika has the rights to develop and commercialize the compound. Newron's additional projects are based on highly promising treatments for rare disease patients and are at various stages of clinical development, including sarizotan for patients with Rett syndrome, sNN0031 for patients with Parkinson's disease, non-responsive to oral drug treatments, sNN0029 for patients with ALS and ralfinamide for patients with specific rare pain indications. Newron is also developing NW-3509 as the potential first add-on therapy for the treatment of patients with positive symptoms of schizophrenia. www.newron.com

About Zambon

Zambon is a leading Italian pharmaceutical and fine-chemical multinational company that has earned a strong reputation over the years for high quality products and services. Zambon is well-established in 3 therapeutic areas: respiratory, pain and woman care, and is very strongly committed to its entry into the CNS space. Zambon SpA produces high quality products thanks to the management of the whole production chain which involves Zach (Zambon chemical), a privileged partner for API, custom synthesis and generic products. The Group is strongly working on the treatment of the chronic respiratory diseases as asthma and BPCO and on the CNS therapeutic area with Xadago™ (safinamide) for the Parkinson treatment. Zambon is headquartered in Milan and was established in 1906 in Vicenza. Zambon is present in 15 countries with subsidiaries and more than 2,600 employees with manufacturing units in Italy, Switzerland, France, China and Brazil. Zambon productes are commercialized in 73 countries.
For details on Zambon please see: www.zambongroup.com

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