



**NEWRON PHARMACEUTICALS REPORTS NEW DATA INDICATING THAT ITS NOVEL ION CHANNEL BLOCKER, RALFINAMIDE, MAY HAVE PREEMPTIVE AND PALLIATIVE ANALGESIC POTENCY AGAINST SPONTANEOUS NEUROPATHIC PAIN**

**Milan, Italy – September 14, 2006** – Newron Pharmaceuticals SpA, a research and development company focused on novel CNS therapies, today announces positive results from a preclinical study showing preemptive and palliative analgesic effects of ralfinamide against spontaneous chronic pain in a rodent model of neuropathy. The study was conducted by Professor Ze'ev Seltzer, Canada Senior Research Chair in Genetics of Pain, University of Toronto, and will be presented at the Fifth Congress of the European Federation of IASP Chapters (EFIC) Istanbul, Turkey, September 14, 2006.

Spontaneous pain was induced in the rat by neurectomy of the sciatic and saphenous nerves unilaterally (Neuroma Model). Ralfinamide significantly and dose-dependently suppressed the spontaneous pain behavior, expressed as self mutilation of denervated hindpaw. While previous data indicated that ralfinamide has analgesic properties in animal models of stimulus-evoked inflammatory and neuropathic pain, this study tested whether ralfinamide can also suppress the spontaneous component of chronic pain – a symptom that is the main complaint of patients seeking medical help for chronic pain.

Using this model, Professor Seltzer's research team report that ralfinamide showed both *preemptive* and *palliative* effects. In fact ralfinamide significantly delayed the onset of spontaneous pain behavior when administered preoperatively for seven days compared to animals receiving no treatment. "If this preemptive analgesic effect is translated to humans, preoperative administration of ralfinamide could prevent pain in people after surgery and perhaps also speed up recovery, minimize chronic pain and reduce postoperative morbidity", said Professor Seltzer.

In addition, his team showed that when ralfinamide was administered postoperatively, through the period of spontaneous pain development after neurectomy (for 42 days), it had a palliative analgesic effect demonstrating that ralfinamide both significantly delayed the onset and decreased the pain scores in a dose-related manner. Furthermore, the analgesic effect outlasted the treatment period of 42 days, since pain scores remained significantly suppressed until the end of the observation period (postoperative day 63).

In a parallel electrophysiological study, Dr Seltzer's team demonstrated that ralfinamide's analgesic effect is achieved by differentially blocking abnormal ectopic inputs generated in sensory fibers caught at a nerve-end neuroma, without affecting normal nerve function. "These results indicate that ralfinamide may be a safe analgesic in humans and suggest its potential use for chronic pain in nerve-injured individuals and in patients with neuropathies" said Patricia Salvati, VP Discovery at Newron Pharmaceuticals.

**About Spontaneous Neuropathic Pain**

Neuropathic pain is a type of chronic pain caused by a lesion to the nervous system. Some neuropathic pain results as an unavoidable side effect of therapy, such as following surgical removal of a malignant tumor or chemotherapy. Total damage to a peripheral nerve results in the production of a nerve-end neuroma. Even a partial nerve injury, such as a near-miss injury,



metabolic diseases like diabetes mellitus, exposure to toxins or drugs, such as certain anti-cancer chemotherapies, result in the formation of a partial neuroma (also termed a neuroma “incontinuity”). The cell body of damaged sensory neurons respond to the injury by down-regulating the expression levels of some membrane ion channels, and up-regulate a number of other channel subunits, including some types that are not observed in intact sensory neurons, resulting in profound changes in excitability. These changes underlie the generation of abnormal input discharges from the damaged sensory neurons resulting in neuropathic pain sensation, both spontaneous and stimulus-evoked. Shutting them off selectively, without affecting normal nerve function, has been the ‘holy grail’ of neuropathic pain treatment. Conditions associated with a high incidence of neuropathic pain include diabetes, post-herpetic neuralgia and others, affecting many millions world wide. On this basis, ralfinamide may provide a treatment choice in neuropathic pain conditions that notoriously do not respond well to conventional pain therapy.

### **About ralfinamide**

Ralfinamide is a potent voltage- and use-dependent ion channel blocker that showed good activity in several animal models of chronic pain. In addition, it has showed promising results in a pilot Phase II clinical trial, where ralfinamide was well tolerated up to the maximal dose with absence of any consistent pattern of clinically-relevant adverse events regarding vital signs, ECG and other laboratory values. Using the Visual Analog Scale (VAS) to measure pain levels before (‘baseline’) and after ralfinamide treatment, a statistically significant improvement in pain was recorded, reducing the average pain level by 26% compared to the baseline levels.

In 2006, Newron initiated a randomised, ascending dose, double-blind, placebo-controlled, dose-titration phase II study with 200 patients in 31 centres in five European countries. The study’s objectives are to determine safety and tolerability and preliminary evidence of efficacy in the dose range for patients with mixed peripheral neuropathic pain.

### **About Newron Pharmaceuticals**

Newron Pharmaceuticals S.p.A (<http://www.newron.com>) is a research and development company focused on novel therapies for diseases of the Central Nervous System (CNS), particularly pain and Parkinson’s disease. Newron is undertaking phase III trials with safinamide, a unique molecule with multiple mechanisms of action, for the treatment of Parkinson’s disease. Preliminary results of a six-month phase III trial have demonstrated benefit in motor symptoms and activities of daily living quality, as well as improvement in cognitive function and good tolerability. Phase II trials with safinamide in Restless Leg Syndrome (RLS) have shown promising results. Newron continues to conduct phase II trials with ralfinamide for the treatment of neuropathic pain. Newron’s clinical pipeline is supported by a broad portfolio of early stage proprietary compounds generated by its ion channel drug discovery platform. Newron is headquartered in Bresso, near Milan, Italy.

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