

**NOVEL ONCE DAILY ANTI-EPILEPTIC ZEBINIX®
APPROVED IN THE EUROPEAN UNION**

New option for treatment of epilepsy patients with partial onset seizures

Bial-Portela & CA, S.A., (S. Mamede do Coronado, Portugal, President & CEO Dr Luis Portela), and Eisai Europe Limited (London; Chairman & CEO Yutaka Tsuchiya), the European subsidiary of Eisai Co., Ltd. (Tokyo, President & CEO: Haruo Naito), today announced that the novel once daily anti-epileptic Zebinix®* (eslicarbazepine acetate) received marketing authorisation from the European Commission as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalisation.

Epilepsy is one of the most common neurological diseases, affecting approximately 1 in 100 people. Treatment of partial-onset seizures, the most common type of epilepsy, remains a constant challenge and up to 40% of patients with partial seizures do not achieve seizure control with current anti-epileptics¹.

The efficacy, safety and tolerability of eslicarbazepine acetate (ESL) has been demonstrated in three phase III double-blind, randomised placebo-controlled trials in 1,049 patients with partial onset seizures²⁻⁴. For each randomised control trial patients were given the option of entering a one year open label extension study.

ESL demonstrated significant and sustained reductions in seizure frequency and significant increases in responder rates (≥50% decrease in seizure frequency.) These studies also demonstrated that patients continued to take ESL with retention rates ranging from 68-79% at one year⁵⁻⁷. The median daily dose throughout this one year treatment was 800mg. Treatment-emergent adverse events affecting >10% of patients in the pivotal studies were dizziness, headache and somnolence⁸.

The studies found that patients taking ESL also showed statistically significant improvement in scores of health related quality of life measures such as reduced 'seizure worry', improvements in 'cognitive functioning' and reduced 'medication effects', all factors which significantly affect the lives of patients living with epilepsy.⁹⁻

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ESL can be given as a true one tablet once a day regimen at its median daily dose as defined in clinical trials as 800mg⁵⁻⁷. It works by selectively inhibiting the rapid firing of neurones. ESL interacts with site two of the voltage-gated sodium channel, stabilising its inactive form and preventing its return to the active open state, thereby

reducing repetitive neuronal firing. ESL has a much higher affinity for the inactivated state of the channel compared with the resting state which means it is less likely to interfere with normal neuronal function ¹².

“A significant number of patients with partial-onset seizures remain uncontrolled on existing epilepsy therapies and the inability to control seizures can have a devastating impact on the quality of a patient’s day to day life and functioning,” said Professor Christian Elger, Director and Head of the Department of Epileptology at the University of Bonn, Germany and the lead author of one of the pivotal studies – published earlier this year in *Epilepsia*.

Under the terms of a deal with Bial announced in February this year, Eisai received a sole license to market, promote and distribute ESL within Europe**.

“The EU approval of Zebinix[®] represents a significant milestone for Bial in our efforts to bring this novel treatment to patients with partial-onset seizures”, said Luís Portela, President and Chief Executive Officer of Bial. “We will work closely with our European partner Eisai to launch Zebinix[®] across the EU during 2009 and into 2010.”

Yutaka Tsuchiya, Chairman & CEO of Eisai Europe said “The effective treatment of patients with partial-onset seizures remains a major challenge for clinicians and the carers of patients with epilepsy, and we are delighted to be working with Bial towards bringing to patients such a promising new treatment for epilepsy. Zebinix[®] joins our existing family of anti-epileptics, which includes zonisamide and rufinamide and a new molecule currently entering phase three clinical development studies. When launched, Zebinix[®] will help us to fulfil our Corporate mission of ‘human health care’ (*hhc*); to provide innovative, high quality medicines to meet the ever changing unmet medical needs of patients and their families as well as health care professionals.”

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Notes to Editors

* **Zebinix**[®] is the EU trade name for eslicarbazepine acetate.

** European Territories

Austria, Belgium, Bulgaria, Czech Republic, Belarus, Bosnia, Croatia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Monaco, Netherlands, Norway, Poland, Romania, Russia, Serbia, Slovakia, Slovenia, Spain (co promotion with Bial from launch) Sweden, Switzerland, Turkey, Ukraine and United Kingdom.

About epilepsy, partial-onset seizures and their treatment

Epilepsy is one of the most common neurological diseases, affecting approximately 1 in 100 people.

Epilepsy is a chronic neurological disease characterised by abnormal discharges of neuronal activity causing seizures. Clinically, these manifest as convulsions or jerking of muscles. Depending on the seizure type, seizures may be limited to one part of the body, or may be generalised to involve the whole body. Patients may also experience abnormal sensations, altered behaviour or altered consciousness. Epilepsy is a disorder with many possible causes. Often the cause of epilepsy is unknown. However, anything that disturbs the normal pattern of neuron activity - from illness to brain damage to abnormal brain development, can lead to seizures.

Epilepsy is characterised by abnormal firing of impulses from nerve cells in the brain. In partial-onset seizures, these bursts of electrical activity are initially focused in specific areas of the brain, but may become more generalised; the symptoms vary according to the affected areas. Nerve impulses are triggered via voltage-gated sodium channels in the nerve cell membrane.

Treatment of partial-onset seizures, the most common type of epilepsy, presents a constant challenge – up to 40% of patients with partial-onset seizures do not achieve seizure control with current anti-epileptic drugs.¹

Furthermore, adverse events, such as lightheadedness (dizziness), somnolence (sleepiness), and cognitive slowing, are highly prevalent with existing anti-epileptic agents and may affect as many as 97% of patients. Hence, there is a need for new anti-epileptic agents that offer effective reduction in seizure frequency combined with a favourable safety profile.

About Eslicarbazepine Acetate

Eslicarbazepine acetate (ESL) is a novel voltage-gated sodium channel blocker. It specifically targets the inactivated state of the ion channel, preventing its return to the active state, and thereby reduces repetitive neuronal firing. The efficacy of ESL has been demonstrated in 3 randomised, placebo controlled studies in 1049 patients with refractory partial onset seizures. ESL also significantly improved patient's health related quality of life (HRQoL) as measured by the QOLIE-31 score during a one year open label extension of the above 3 studies. ESL is given orally once daily. ESL can be used as an add-on to carbamazepine (one of the most commonly utilized therapies for partial onset seizures) or with other anti-epileptics.

Clinical data

The EU approval was based on data from phase II and three phase III, double-blind, randomised, placebo-controlled, multi-centre trials involving 1,192 patients from 23 countries. Patients had a history of at least four partial seizures per month despite treatment with up to three concomitant anti-epileptic drugs.

During the trials, patients were randomised to various dosages of ESL or placebo and after a 2-week titration period, were assessed over a 12 week maintenance period, with continued follow-up over a one year open-label period.

Efficacy

Over the 12 week maintenance period, ESL 800mg and 1200mg once-daily reduced seizure frequency by over one third,⁸ and was significantly more effective than placebo. This significant decrease in seizure frequency was sustained over the one-year open label treatment period and was consistent regardless of baseline therapy.

Tolerability

The safety profile of ESL was favourable. The majority of treatment related adverse events were mild or moderate in intensity. After 6 weeks of treatment, there were no observed differences in the incidence of side effects between patients treated with ESL and the placebo group.⁸

Quality of life and depressive symptoms

The effect of ESL on quality of life was assessed using the Quality of Life Epilepsy Inventory-31 (QOLIE-31) scale. There was a statistically and clinically significant improvement from baseline during long-term open-label therapy, including a mean relative improvement in overall quality of life ($p < 0.001$ – $p < 0.01$ across the three studies) and improvements in individual elements of the QOLIE-31 scale including seizure worry, emotional wellbeing, energy/fatigue, medication effects and social function.

Improvement in depressive symptoms was also measured using the Montgomery Asberg Depression Rating Scale (MADRS). During long-term, open-label therapy, ESL demonstrated a statistically significant improvement from baseline in the overall MADRS score ($p < 0.0001$) and individual domains of the MADRS scale including pessimistic thoughts, concentration difficulties, apparent sadness and inner tension.

These data were presented at the 8th European Congress on Epileptology held in Berlin last September 2008 and at the Annual Meeting of the American Epilepsy Society (AES) in December 2008, Seattle, WA, USA.

About Bial

Founded in 1924, Bial is an international pharmaceutical group with products available in over 30 countries throughout four continents. BIAL is the largest Portuguese pharmaceutical company and is based in S. Mamede do Coronado, Portugal.

It is the partner of choice for many companies, having a strong presence in the Iberian peninsula as well as in over 10 countries in Latin America and in around 20 French or Portuguese speaking African countries.

Bial is strongly committed to therapeutic innovation investing approximately 20% of its turnover in research and development every year. Key research areas for BIAL are the central nervous system, the cardiovascular system and allergology. Bial currently has several other innovative programs under development, which the company expects to bring to the market within the next years, thereby strengthening its position throughout Europe.

Further information about Bial can be found at www.bial.com

About Eisai

Eisai is one of the worlds leading R&D-based pharmaceutical companies, that has defined its corporate mission as “giving first thought to patients and their families and

to increasing the benefits health care provides,” which we call *human health care (hhc)*.

Eisai concentrates its R&D activities in three key areas

- **Integrative Neuroscience:** Alzheimer’s disease, multiple sclerosis, neuropathic pain, epilepsy, depression, etc
- **Integrative Oncology: Anticancer therapies;** tumour regression, tumour suppression, antibodies, etc and **Supportive cancer therapies;** pain relief, nausea, etc
- **Vascular/Immunological Reaction:** Acute coronary syndrome, atherothrombotic disease, sepsis, rheumatoid arthritis, psoriasis, Crohn’s disease, etc

With operations in the U.S., Asia, Europe and its domestic home market of Japan, we employ more than 10,000 people worldwide, and reported consolidated sales of over £3.53 billion in FY2007, an increase of 8.9% year on year. In Europe, Eisai undertakes sales and marketing operations in over 20 markets, including the United Kingdom, France, Germany, Italy, Spain, Switzerland, Sweden, Ireland, Austria, Denmark, Finland, Norway, Portugal, Iceland, Czech Republic, Hungary, and Slovakia.

For further information please visit our web site www.eisai.co.jp

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