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ZEBINIX A NOVEL ONCE DAILY ANTI-EPILEPTIC LAUNCHED TODAY IN THE UK

New option for adjunctive treatment of adult epilepsy patients with partial onset seizures reduces seizure frequency and improves health-related quality of life

Eisai (London; Managing Director Nick Burgin), today announced that the novel once daily anti-epileptic Zebinix[®] (eslicarbazepine acetate) was launched in the UK 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 – and the successful treatment of partial-onset seizures (the most common type of epilepsy) remains a challenge. Up to 40% of patients with partial seizures do not achieve seizure control with current anti-epileptics¹.

Developed from the current 'gold standard' treatment carbamazepine (launched in 1965), Zebinix (eslicarbazepine acetate) offers patients improved seizure control with a favourable safety profile. Patients also report improvements in health-related quality of life measures such as 'seizure worry' and 'cognitive function' as well as improvement in the MADRS (Montgomery-Asberg Depression Rating Scale) depressive symptoms scale. Depression is often reported by patients with poorly controlled epilepsy.

"Epilepsy continues to place a huge burden on individuals with the condition across the UK. Unfortunately despite advances in treatment and investigation many such patients continue to have seizures. Continued seizures bring significant risk of poor quality of life, reduced employment and the development of mental illness such as depression or anxiety. New drugs offer potential hope and choice for these patients. The launch of eslicarbazepine acetate should offer a new choice for patients and clinicians in reducing the burden of epilepsy," said Mike Kerr, Professor of learning disabilities at Cardiff University, who has a special interest in the treatment and psychological impact of epilepsy.

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 adult 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.

In these studies eslicarbazepine acetate demonstrated significant and sustained reductions in seizure frequency and significant increases in responder rates. These studies also demonstrated that patients continued to take eslicarbazepine acetate 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 somnolence.⁸

Eslicarbazepine acetate is also novel in that it 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.

Eslicarbazepine acetate is a voltage gated sodium channel blocker that has a higher affinity for the inactivated state of the channel compared with the resting state. This suggests an enhanced inhibitory selectivity for rapidly firing neurons over those displaying normal activity⁹. Eslicarbazepine acetate has been developed to avoid formation of the epoxide metabolite which has been associated with neurological side effects.

Nick Burgin, Managing Director Eisai in the UK, said “The effective treatment of patients with partial-onset seizures remains a major challenge for clinicians as well as for patients with epilepsy and their families. We are delighted to be bringing patients such a promising new treatment. The launch of eslicarbazepine acetate will further help us to fulfil our Corporate mission of ‘human health care’ (*hhc*) by providing 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.

Zebinix[®] is under license from Bial.

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. 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 is indicated as adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation. 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 1,049 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. Treatment-emergent adverse events affecting >10% of patients in the pivotal studies were dizziness, headache and somnolence.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.¹⁰⁻¹²

License Agreement

Eisai Europe Limited (Headquarters: London, President & CEO: Folker Kindl), a European subsidiary of Eisai Co., Ltd. (Headquarters: Tokyo, President & CEO: Haruo Naito), announced in February this year that it had entered into a license and co-promotion agreement with Bial - Portela & C^a, S.A. (Headquarters: São. Mamede do Coronado, Portugal, CEO: Luís Portela, "Bial"), which gave Eisai Europe Limited. rights to sell Bial's anti-epileptic drug Zebinix[®] (eslicarbazepine acetate) in Europe.

About Eisai

Eisai is one of the world's 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

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

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