News

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Vimpat® (lacosamide) significantly reduced partial onset seizures regardless of the mechanism of action of concomitant antiepileptic drugs

Comprehensive lacosamide analyses published in CNS Drugs

- Pooled phase II/III clinical trial data demonstrated efficacy and tolerability of lacosamide as adjunctive treatment of partial onset seizures
- Post-hoc exploratory analyses showed seizures reduced in patients whether lacosamide was added to antiepileptic drug (AED) regimens containing at least one "traditional" sodium channel blocking AED or to regimens not containing "traditional" sodium channel blocking AEDs

Brussels (Belgium), 12th January 2011, 1800 CET – Comprehensive analyses of pooled data from three randomized, double-blind, placebo-controlled Phase II/III trials showing the efficacy and tolerability of Vimpat® (lacosamide) for patients with partial onset seizures, regardless of the type of concomitant AED used, have been published in the drug evaluation journal, *CNS Drugs.*[3,4]

Two key papers have reported that adjunctive lacosamide reduced seizures and improved responder rates compared to placebo, with tolerability data consistent with previous observations in individual trials.

"Analyses of multiple, individual trials with similar design provide a valuable opportunity to evaluate clinically relevant aspects of the resulting large patient pool. These analyses showed the efficacy of lacosamide in combination therapy regardless of existing AED used and support the use of lacosamide as adjunctive therapy with a broad range of AEDs," commented Dr Steve Chung, Barrow Neurological Institute, Phoenix, Arizona, US.

Lacosamide (film-coated tablets, syrup and solution for infusion) was launched in the European Union in September 2008, as adjunctive therapy for the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy, aged 16

years and older. Lacosamide solution for infusion may be used when oral administration is temporarily not feasible.

In the US, Vimpat® tablets and injection were launched in May 2009 as an add-on therapy for the treatment of partial-onset seizures in people with epilepsy who are 17 years and older. Lacosamide injection is a short-term replacement when oral administration is not feasible in these patients. Lacosamide oral solution was launched in June 2010. The availability of the oral tablets, oral solution, and intravenous (IV) injection allows for consistent treatment in a hospital setting. The most common adverse reactions occurring in 10 percent or more of lacosamide-treated patients, and greater than placebo, were dizziness, headache, nausea, and diplopia. Additional important safety information for lacosamide is available at the end of the press release.

The maximum recommended daily dose for Vimpat® in the European Union and the US is 400 mg/day. The 600mg/day dose is not an approved or recommended dose in the European Union or in the US.[1,2]

Clinical utility of lacosamide – pooled analysis of phase II/III clinical trials[3]
Pooled data from three phase II/III trials with 1294 difficult to treat patients with partial onset seizures with or without secondary generalization showed significantly greater reductions in median seizure frequency with adjunctive lacosamide compared to placebo, together with significantly higher 50% and 75% responder rates. In these trials, patients were randomized to placebo or lacosamide administered twice daily in equally divided doses with weekly titration in 100 mg/day increments to the assigned target dose (200, 400, or 600 ₸ mg/day), followed by a 12 week maintenance phase.

Lacosamide showed a significant improvement compared to placebo for:

- Median percent seizure reduction (intention to treat [ITT] and intention to treat during the 12 week maintenance phase [ITTm]: $p < 0.05$ for 200 mg/day, $p < 0.001$ for 400 and 600 ₸ mg/day)
- 50% responder rate (ITT and ITTm: $p < 0.05$ for 200 mg/day, $p < 0.001$ for 400 and 600 ₸ mg/day).

Secondary variable findings were:
- Significantly more patients randomized to lacosamide 400 or 600 ₸ mg/day achieved a ≥75% reduction in seizure frequency compared to placebo (ITT and ITTm; $p < 0.001$)

- Seizure freedom in 2.7%, 3.3% and 4.8% of patients completing the maintenance phase in the lacosamide 200, 400 and 600 ₮ mg/day groups, respectively, with no seizures throughout the entire maintenance phase (placebo group = 0.9%)
- Mean changes from baseline in seizure-free days in patients entering the maintenance phase were 8.0%, 11.6% and 14.7% with lacosamide 200 (p=0.077), 400 (p<0.001) and 600 ₮ (p<0.001) mg/day groups, respectively, compared with 6.1% in the placebo group

Post hoc findings were:

- Efficacy advantages of lacosamide over placebo by the end of the first week of treatment
- Similar efficacy in lacosamide-treated patients reporting prior surgical intervention for epilepsy compared to lacosamide-treated patients with no prior surgical intervention
- Reduction in seizures with lacosamide, regardless of concomitant AEDs used
- Support for the therapeutic dose range of lacosamide, with no additional safety concerns identified (pharmacokinetic-pharmacodynamic model)

In this pooled analysis four treatment emergent adverse events (dizziness 31% vs 8%, headache 13% vs 9%, nausea 11% vs 4% and diplopia 11% vs 2%) occurred at an incidence of ≥10% in the lacosamide total group (all dosages) and greater than placebo. Treatment emergent adverse events leading to discontinuation with an incidence of greater than 5% in any treatment group were dizziness and coordination abnormalities (ataxia), which were both associated with the 600 ₮ mg/day group.

Pooled analysis by mechanism of action of concomitant antiepileptic drug[4]

A *post hoc* exploratory analysis of data on 1308 patients from the pooled phase II/III trials was carried out to evaluate the efficacy and tolerability of lacosamide, based upon the inclusion or non inclusion of at least one "traditional" sodium channel blocking AED (defined as carbamazepine, lamotrigine, oxcarbazepine, and phenytoin derivatives).

Eighty two per cent of patients were using at least one "traditional" sodium channel blocking AED as part of their concomitant AED regimen. In this subgroup of patients, adjunctive lacosamide significantly reduced seizure frequency (p<0.01, 200, 400 and 600 ₮ mg/day) and significantly increased 50% and 75% responder rates (p<0.01, 400 mg/day; p<0.01 [50% responder rate] and p<0.05 [75% responder rate] for 600 ₮ mg/day) compared to placebo, with improvements similar to those seen in the full pooled Phase II/III population.

- In the full pooled population, the median percent reduction in seizure frequency per 28 days for current therapy and placebo, lacosamide 200 mg/day, 400 mg/day and 600 ₸ mg/day were 19.2%, 33.5%, 41.4% and 48.8% ($p<0.01$ all lacosamide doses vs placebo). These compared with 18.9%, 33.3%, 39.0% and 42.7% ($p<0.01$ all doses) in the sub group using at least one "traditional" sodium channel blocking agent
- In the full pooled population, 50% responder rates for current therapy and placebo, lacosamide 200 mg/day, 400 mg/day and 600 ₸ mg/day were 23.1% , 34.8% ($p<0.05$), 44.3% ($p<0.01$) and 48.6% ($p<0.01$) respectively. These compared with 22.7%, 33.3%, 39.9% ($p<0.01$) and 42.4% ($p<0.01$) respectively in the sub group using at least one "traditional" sodium channel blocking AED.

Treatment emergent adverse events (TEAEs) and discontinuations due to TEAEs in this subgroup were dose-related and occurred at a similar incidence to the pooled Phase II/III population. The most common TEAEs (incidence ≥5% for all lacosamide doses combined and greater than placebo) were dizziness, headache, nausea and diplopia.

In the remaining 18% (n=231) of patients not taking any "traditional" sodium channel blocking AEDs as part of their concomitant AED regimen, a pronounced, dose-related seizure reduction was observed when lacosamide was added ($p<0.01$, 400 and 600 ₸ mg/day for median percent seizure reduction and 50% or 75% responder rates).

- The median % reduction in seizure frequency per 28 days for current therapy and placebo, lacosamide 200 mg/day, 400 mg/day and 600 ₸ mg/day exceeded those seen with the full pooled population: 28.0%, 38.0%, 62.5% ($p<0.01$) and 79.0% ($p<0.01$), respectively).
- The 50% responder rates for current therapy and placebo, lacosamide 200 mg/day, 400 mg/day and 600 ₸ mg/day exceeded those seen with the full pooled population: 25.0%, 41.9%, 62.3% ($p<0.01$) and 79.2% ($p<0.01$), respectively).

The TEAEs occurring with an incidence of ≥10% (placebo vs total lacosamide) were dizziness 7.4% vs 15.3%, headache 10.3% vs 12.3% and fatigue 5.9% vs 10.4%. In contrast to the sub-group taking "traditional" sodium channel blocking AEDs, there was no dose relationship for discontinuations due to TEAEs suggesting a potential for improved tolerability.

Commenting on the post hoc analyses Dr John-Kenneth Sake, Head Epilepsy, Global Medical Affairs, UCB, said "The nature of the analyses and the small sample size in the sub-group not taking any "traditional" sodium channel blocking AEDs suggests the need

for prospectively designed trials to better evaluate the potential for additive or synergistic effects of various AED combinations."

Ŧ The maximum recommended daily dose for Vimpat® in the European Union and the US is 400 mg/day. The 600mg/day dose is not a recommended dose in the European Union on in the US.[1,2]

References

1. Lacosamide Summary of Product Characteristics (EU) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000863/WC500050338.pdf (Accessed 27th October 2010)

2. Vimpat® Prescribing Information (US) http://www.vimpat.com/prescribing-information.aspx

3. Chung S, Ben-Menachem E, Sperling MR, Rosenfeld W, Fountain NB, Benbadis S, Hebert D, Isojärvi J, Doty P. Examining the Clinical Utility of Lacosamide. CNS Drugs 2010; 24 (12): 1055-1068

4. Sake J-K, Hebert D, Isojarvi J, Doty P, De Backer M, Davies K, Eggert-Formella A, Zackheim J. A Pooled Analysis of Lacosamide Clinical Trial Data Grouped by Mechanism of Action of Concomitant Antiepileptic Drugs. CNS Drugs 2010; 24(12): 1055-1068

Important safety information about lacosamide in the EU and EEA

Lacosamide is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy aged 16 years and older. Lacosamide solution for infusion is an alternative for patients when oral administration is temporarily not feasible. Contraindications: Hypersensitivity to the active substance or any of the excipients; known second- or third-degree atrioventricular (AV) block. Special warnings and precautions for use: Treatment with lacosamide has been associated with dizziness which could increase the occurrence of accidental injury or falls. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicine. Prolongations in PR interval with lacosamide have been observed in clinical studies. Cases with second and third degree AV block associated with lacosamide treatment have been reported in post-marketing experience. Lacosamide should be used with caution in patients with known conduction problems or severe cardiac disease such as a history of myocardial infarction or heart failure. Caution should especially be exerted when treating elderly patients as they may be at an increased risk of cardiac disorders or when lacosamide is used in combination with products known to be associated with PR prolongation. Suicidal ideation and behavior have been reported in patients treated with anti-epileptic agents. Therefore patients should be monitored for signs of suicidal ideation and behaviors and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge. Lacosamide syrup contains sodium methylhydroxybenzoate (E219), which may cause allergic reaction (possibly delayed).

Patients with rare hereditary problems of fructose intolerance should not take this medicine. The syrup contains aspartame (E951), a source of phenylalanine, which may be harmful for people with phenylketonuria. Both the syrup and solution for infusion contain sodium. To be taken into consideration for patients on a controlled sodium diet. Effects on ability to drive and use machines: Lacosamide may have minor to moderate influence on the ability to drive and use machines. Lacosamide treatment has been associated with dizziness and blurred vision. Accordingly patients should be advised not to drive a car or to operate other potentially hazardous machinery until they are familiar with the effects of lacosamide on their ability to perform such activities. Laboratory abnormalities: Abnormalities in liver function tests have been observed in controlled trials with lacosamide in adult patients with partial-onset seizures who were taking 1-3 concomitant antiepileptic drugs. Elevations of ALT to ≥3XULN occurred in 0.7% (7/935) of lacosamide patients and 0% (0/356) of placebo patients. Multiorgan Hypersensitivity Reactions: Multiorgan hypersensitivity reactions have been reported in patients treated with some antiepileptic agents. These reactions are variable in expression but typically present with fever and rash and can be associated with involvement of different organ systems. Potential cases have been reported rarely with lacosamide and if multiorgan hypersensitivity reaction is suspected, lacosamide should be discontinued. Undesirable effects: The most common adverse reactions (≥10 %) are dizziness, headache, diplopia, and nausea. Other common adverse reactions (1–<10 %) are depression, confusional state, balance disorder, coordination abnormal, memory impairment, cognitive disorder, somnolence, tremor, nystagmus, hypoesthesia, dysarthria, disturbance in attention, vision blurred, vertigo, tinnitus, vomiting, constipation, flatulence, dyspepsia, dry mouth, pruritus, rash, muscle spasms, gait disturbance, asthenia, fatigue, irritability, injection site pain or discomfort (specific to solution for infusion), irritation (specific to solution for infusion), fall, and skin laceration. Refer to the European Summary of Product Characteristics for other adverse reactions and full prescribing information. Date of revision 25th October 2010

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000863/WC500050338.pdf (Accessed 27th October 2010)

Important safety information about Vimpat® in the U.S.

Warnings and Precautions

AEDs increase the risk of suicidal behavior and ideation. Patients taking Vimpat® should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Patients should be advised that Vimpat® may cause dizziness, ataxia, and syncope. Caution is advised for patients with known cardiac conduction problems, who are taking drugs known to induce PR interval prolongation, or with severe cardiac disease. In patients with seizure disorders, Vimpat® should be gradually withdrawn to minimize the potential of increased seizure frequency. Multiorgan hypersensitivity reactions have been reported with AEDs. If this reaction is suspected, treatment with Vimpat® should be discontinued.

For full prescribing information on Vimpat®, visit http://www.vimpat.com/prescribing-information.aspx, and for more information on Vimpat®, visit Vimpat.com or contact UCB at (800) 477-7877.

Vimpat® is a Schedule V controlled substance.

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About UCB
UCB, Brussels, Belgium (www.ucb.com) is a global biopharmaceutical company focused on the discovery and development of innovative medicines and solutions to transform the lives of people living with severe diseases of the immune system or of the central nervous system. With more than 8,000 people in about 40 countries, the company generated revenue of EUR 3.1 billion in 2009. UCB is listed on Euronext Brussels (symbol: UCB).

Forward-looking statements
This press release contains forward-looking statements based on current plans, estimates and beliefs of management. Such statements are subject to risks and uncertainties that may cause actual results to be materially different from those that may be implied by such forward-looking statements contained in this press release. Important factors that could result in such differences include: changes in general economic, business and competitive conditions, effects of future judicial decisions, changes in regulation, exchange rate fluctuations and hiring and retention of its employees.