Nobelpharma Co., Ltd. Eisai Co., Ltd.

## Nobelpharma and Eisai Announce Japan Launch of Anticonvulsant Agent Fostoin® 750 mg for Injection

Nobelpharma Co., Ltd. (Headquarters: Tokyo, President & CEO: Jin Shiomura, "Nobelpharma") and Eisai Co., Ltd. (Headquarters: Tokyo, President & CEO: Haruo Naito, "Eisai") announced today that they will launch the anticonvulsant agent Fostoin<sup>®</sup> 750 mg for Injection (fosphenytoin sodium hydrate, "fostoin") on January 17. Developed in Japan by Nobelpharma, Fostoin<sup>®</sup> will be marketed by Eisai and co-promoted by both companies under a previously concluded marketing agreement.

Fostoin<sup>®</sup> is a water-soluble prodrug of phenytoin injection, a drug that has long been used both in Japan and overseas as a treatment for status epilepticus and other such conditions. By providing phenytoin as a water-soluble prodrug, the agent will significantly reduce local irritation during intravenous infusion and is expected to enhance tolerability. Fostoin<sup>®</sup> was approved in Japan as a clinically beneficial treatment on July 1, 2011, and was subsequently listed on Japan's National Health Insurance (NHI) drug reimbursement price list on November 25.

Fostoin® was designated as a drug for which here is a significant medical need by the Japanese Ministry of Health, Labour and Welfare's "Study Group on Unapproved Drugs," the predecessor to the "Study Group for Unapproved and Off-label Drugs for Which There is an Medical Need," in July 2006. The Group determined that Fostoin® should not only be used to control status epilepticus, but that it was also necessary in the prevention and treatment of epileptic seizures occurring during neurosurgery or head injury and as an alternative treatment when other means of phenytoin, including oral phenytoin, are unavailable or inappropriate, two indications already approved overseas. It also recommended that clinical trials with the agent in Japan should begin as soon as possible. Following this recommendation, Nobelpharma developed Fostoin® in Japan, and submitted a Manufacturing and Marketing Authorization Application seeking approval of the agent to the MHLW in June 2010.

Nobelpharma is proactively undertaking the development of drugs for which patient groups and academic societies have deemed necessary and there is a high unmet medical need, while Eisai defines epilepsy as a therapeutic area of focus and seeks to enhance its Japanese product portfolio in this field by developing new anti-epilepsy agents. Both Nobelpharma and Eisai will strive to make contributions to address the diversified needs of, and increase the benefits provided to, patients and families suffering from seizures associated with conditions such as epilepsy.

# [Please refer to the attached notes for further information on Fostoin® 750 mg for Injection, Eisai's Commitment to Epilepsy and epilepsy, as well as a glossary of terms.]

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#### **Notes to Editors**

## 1. About Fostoin® 750 mg for Injection

Fostoin® 750 mg for Injection (fosphenytoin sodium hydrate) is a water soluble prodrug of phenytoin that has long been used both in Japan and overseas as a treatment for status epilepticus and other such conditions. It exerts its effects after undergoing rapid alkaline phosphatase (an enzyme found in the blood and organs) catalyzed hydrolyzation to yield its active metabolite phenytoin. By providing phenytoin as a water-soluble prodrug, it is possible to significantly reduce local irritation during intravenous infusion and to enhance tolerability. As of January 2011, Fostoin® is approved in 24 countries, including the United States, the United Kingdom and France, for the control of status epilepticus and the prevention and treatment of seizures occurring during neurosurgery or head injury as well as an alternative treatment when oral administration of phenytoin is unavailable or inappropriate.

#### 2. Product Outline

#### 1) Product Name

Fostoin® 750 mg for Injection

#### 2) Generic Name

fosphenytoin sodium hydrate

#### 3) Indications and Usage

- 1. Status epilepticus
- 2. Suppression of seizure onset during neurosurgery or impaired consciousness (head injury, etc.)
- 3. Temporary alternative therapy for epilepsy patients being administered oral phenytoin

## 4) Dosage and Administration

The following dosage and administration is recommended for adults and children over two years of age

#### 1 . Status epilepticus

Loading Dose

The loading dose of fosphenytoin sodium is 22.5 mg/kg administered intravenously. The dose should be administered no faster than 3mg/kg/minute or 150mg/minute, whichever in lower.

#### Maintenance Dose

The maintenance dose of fosphenytoin sodium is 5~7.5 mg/kg/day administered intravenously as a single dose or divided equally into several doses. The dose should be administered no faster than 1mg/kg/minute or 75mg/minute, whichever in lower.

#### 2 . Suppression of seizure onset during neurosurgery or impaired consciousness (head injury, etc.)

Loading Dose

The loading dose of fosphenytoin sodium is 15~18 mg/kg administered intravenously. The dose should be administered no faster than 1 mg/kg/minute or 75 mg/minute, whichever in lower.

## Maintenance Dose

The maintenance dose of fosphenytoin sodium is 5~7.5 mg/kg/day administered intravenously as a single dose or divided equally into several doses. The dose should be administered no faster than 1mg/kg/minute or 75mg/ minute, whichever in lower.

#### 3 . Temporary alternative therapy for epilepsy patients being administered oral phenytoin

Fosphenytoin sodium should be administered intravenously once daily or divided equally into several doses at a dose equivalent to 1.5 times that of oral phenytoin. The dose should be administered no faster than 1mg/kg/minute or 75mg/minute, whichever in lower.

#### 5) Price

Fostoin<sup>®</sup> 750 mg for Injection 6,299 yen per vial

#### 6) Packaging

Fostoin<sup>®</sup> 750 mg for Injection Two vials

#### 7) Manufacturer:

Nobelpharma Co., Ltd.

#### 8) Distributor:

Eisai Co., Ltd.

#### 3. Eisai's Commitment to Epilepsy

Eisai defines epilepsy as a therapeutic area of focus, currently marketing Zonegran® (under license from the originator Dainippon Sumitomo Pharma Co., Ltd.; sodium/calcium channel blocking antiepileptic agent; marketed in Europe, the United States and Asia) and Zebinix® (under license from the originator BIAL-Portela & Ca S.A.; voltage-dependent sodium channel-blocking antiepileptic agent; marketed in Europe) as adjunctive therapies in adults with partial onset seizures, and Inovelon®/BANZEL® (under license from the originator Novartis AG; sodium channel-blocking novel triazole derived antiepileptic agent; marketed in Europe (Inovelon®), Asia (BANZEL®), and the North America (BANZEL®) for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome, a severe form of early childhood-onset epilepsy.

Marketing authorization applications seeking approval of the AMPA receptor antagonist perampanel as a novel treatment for partial-onset seizures in patients with epilepsy are currently under regulatory review in the United States and European Union (EU). The agent is also being evaluated for the same indication in phase II studies being conducted in Japan as well as in global phase III studies for generalized epilepsy. Eisai also plans to conduct further studies to investigate the potential of perampanel as a monotherapy in partial-onset seizures and for the treatment of other forms of epilepsy such as Lennox-Gastaut syndrome.

By offering multiple treatment options as part of its abundant product lineup, Eisai will continue to make further contributions to address the diversified needs of, and increase the benefits provided to, epilepsy patients and their families.

## 4. Glossary of Terms

#### 1) Epilepsy

Epilepsy is chronic neurological condition that is caused by a variety of factors, and which is characterized by repetitive seizures that are triggered by overactivity of neurons in the brain. During seizures, patients may experience both convulsive and non-convulsive symptoms such as convulsions and loss of consciousness, as well as those that are not always recognized as seizures, such as blank staring, lip smacking, or jerking movements of arms and legs.

Epilepsy can develop at any age and is thought to affect an estimated one million people in Japan.

#### 2) Status epilepticus

Status epilepticus is defined as an unremitting seizure that continues for an extended length of time or short recurrent seizures without regaining consciousness. As status epilepticus may cause severe permanent brain damage in left untreated, the utmost priority is given to suppressing seizures.

#### 3) Convulsive Seizure

Convulsive seizures occur as a result of the brain sending out abnormal signals that are triggered by damage to part of the brain. When these abnormal signals occur in neurons associated with movement, they cause a patient's arms and legs on the side of the body controlled by the respective neurons to contract involuntarily. Most seizures normally subside within several minutes.

#### [Product Photograph]

