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EA Pharma Co., Ltd.
Eisai Co., Ltd.

All-case Surveillance Condition for Approval of "Actonel® 17.5 mg tablets" for Treatment of Paget's Disease of Bone Cleared in Japan

EA Pharma Co., Ltd. (President, Yuji Matsue; Headquarters, Tokyo, Japan) and its parent company Eisai Co., Ltd. (CEO, Haruo Naito; Headquarters, Tokyo, Japan) announced that Japan's Ministry of Health, Labour and Welfare (MHLW) has given notification of the results of reexamination to the effect that the "all-case surveillance" specified drug use-results survey condition required for the approval of "Actonel® 17.5 mg tablets" (risedronate sodium hydrate) indicated for treatment of Paget's disease of bone has been lifted.

In July 2008, MHLW approved the indication for treatment of "Paget's disease of bone" for Actonel 17.5 mg tablets" with the following conditions for approval: "Because of the very limited number of subjects treated in the Japanese clinical trials, the applicant is required to conduct all-case drug use-results survey until data from a certain number of patients are accumulated after market launch, in order to identify the background information of patients treated with the product and collect safety and efficacy data on the product in the early post-marketing period, and thereby take necessary measures to ensure proper use of the product."

Based on the safety data in 307 patients and efficacy data in 276 patients submitted to MHLW as the results of analyses of all-case surveillance, MHLW has concluded that the all-case surveillance was conducted properly and the necessary measures to ensure proper use of the product were being taken sufficiently to lift the condition.

EA Pharma Co., Ltd. and Eisai Co., Ltd. continually strive to promote proper use of the product and provide timely additional information of the product to increase benefits to patients and their families.

End

Media Inquiry	
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More Information

■About "Actonel® 17.5 mg tablets" (risedronate sodium hydrate)

"Actonel®" is a bisphosphonate originally synthesized by Norwich Eaton Pharmaceuticals, Inc. (US) (now Allergan plc). In Japan, "Actonel" launched with indication for once-daily osteoporosis treatment under the brand name of "Actonel 2.5 mg tablets" in May 2002. Later, additional formulations - once-weekly "Actonel 17.5 mg tablets" in June 2007 and once-monthly "Actonel 75 mg tablets" in February 2013 - became available in the market. "Actonel" has contributed significantly to the treatment of patients suffering from osteoporosis. "Actonel 17.5 mg tablets" were further approved for the additional indication for treatment of Paget's disease of bone in July 2008. "Actonel" is manufactured by EA Pharma Co., Ltd. as the marketing authorization holder, and is marketed by Eisai Co., Ltd in Japan.

■About Paget's disease of bone

Paget's disease of bone is a metabolic disorder of the bone. Its etiology is unknown. Paget's disease of bone causes deformity and thickening of the bone due to locally abnormally accelerated bone resorption and subsequent formation. The major symptoms are pain and bone deformation of the affected area. Paget's disease of bone can sometimes complicate osteoarthritis and neurologic symptoms, which can seriously deteriorate QOL of patients. Further, Paget's disease of bone is known to develop to secondary malignant neoplasms including osteosarcoma, and a highly effective treatment is desired. The prevalence of this disease is very low in Japan: 2.8 people out of a population of 1 million, according to a report[1)].

1) Hashimoto J et al., Prevalence and clinical features of Paget's disease of bone in Japan. *Osteoporosis Japan*. 2007; 15(2): 241-245

■About the results of specified (all-case) drug use-result survey

The specified drug use-result survey is conducted for the purpose of collecting and confirming side effect incidence by symptom, quality, efficacy and safety information in pediatric, geriatric, pregnant patients, patients with renal dysfunction, hepatic dysfunction, patients who use the drug for a long time or those patients with any limitations or conditions in drug use. The manufacturing and distributing company of the drug or the like undertakes the clinical survey.

The drug use-result survey specified in this release was conducted by central registration method to investigate the safety and efficacy of "Actonel 17.5 mg tablets" and "Benet 17.5 mg tablets"* in actual drug use under the approved conditions. The patients registered were all the 315 patients who started use of the drug for treatment of Paget's disease of bone within the period from August 2008 through January 2016 and continued administration of the drug once daily for 8 weeks (administration period) with 48 week's observation period in 92 medical facilities located in Japan.

In the 307 safety analytical set, side effects were observed in 15% (46 out of 307 patients). The major side effects were gastrointestinal disorders (6.8%, 21/307 patients) such as nausea (5 cases), abdominal discomfort (4 cases), constipation and dyspepsia (3 cases, respectively), esophagitis and loose stool (2 cases, respectively); metabolism and nutritional disorders (2.3%,

7/307 patients) of hypocalcemia (7 cases); general and systemic disorders and local area symptoms (1.6%, 5/307 patients) of fever (3 cases) and malaise (2 cases); and hepatobiliary disorders (1.3%, 4/307 patients) such as liver dysfunction (2 cases), musculoskeletal and connective tissue disorders (1.0%, 3/307 patients) of back pain (2 cases).

With respect to efficacy, excess serum alkaline phosphatase** changes were similar to the results obtained in the Phase III clinical trial in Japan, and improvement of pain was observed. All bone metabolism markers (urine type I collagen cross-linked N-telopeptide, urine deoxypyridinoline and serum bone alkaline phosphatase) declined as compared with the levels at the initiation of administration.

* Takeda Pharmaceutical Co., Ltd. has obtained manufacturing and marketing approval for Bennet Tablets 17.5 mg (risedronate sodium hydrate).

** Excess serum alkaline phosphatase = actual measurement value of serum ALP －(maximum standard value + minimum standard value)/2

■About EA Pharma Co., Ltd.

EA Pharma Co., Ltd., a subsidiary of Eisai Co., Ltd. for gastrointestinal disease area, was established in April 2016 by integration of the gastrointestinal business unit with more than 60 year's history of the Eisai Group and the gastrointestinal business unit of the Ajinomoto Group having amino acid as its business core. EA Pharma Co., Ltd., is a gastrointestinal specialty pharmaceutical company with a full value chain covering R&D, production & logistics and sales & marketing.

For further information on EA Pharma Co., Ltd.,, please visit http://www.eapharma.co.jp/en/

■About Eisai Co., Ltd.

Eisai Co., Ltd. defines our corporate mission as "giving first thought to patients and their families and to increasing the benefits health care provides," which we call our *human health care* (*hhc*) philosophy. With approximately 10,000 employees working across our global network of R&D facilities, manufacturing sites and marketing subsidiaries, we strive to realize our *hhc* philosophy by delivering innovative products to address unmet medical needs, with a particular focus in our strategic areas of Neurology and Oncology.

As a global pharmaceutical company, our mission extends to patients around the world through working with key stakeholders to improve access to medicines in developing and emerging countries.

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