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Chugai's ALK Inhibitor "Alecensa®" Accelerated Approval in Three Months after Priority Review Designation in the US

TOKYO, December 14, 2015 - Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) announced today that Genentech Inc., a member of the Roche Group, obtained approval from the U.S. Food and Drug Administration (FDA), for the anti-cancer agent, alectinib hydrochloride (brand name: Alecensa®) for the indication of "anaplastic lymphoma kinase (ALK) positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or those intolerant to crizotinib."

"Alecensa was created by Chugai and in July 2014, Japan became the first country in the World to receive approval. We believe that the FDA's priority review of Alecensa will bring fresh hope for patients in the US living with this disease." said Chugai's Director and Executive Vice President, Dr. Yutaka Tanaka. "We are extremely pleased that Alecensa can contribute to the treatment of patients with ALK positive NSCLC."

Alecensa was granted Breakthrough Therapy Designation by FDA in June 2013 for patients with ALK positive NSCLC who have progressed on crizotinib. And FDA also granted priority review for Alecensa in September 2015.

The FDA's Accelerated Approval Program allows conditional approval of a medicine that fills an unmet medical need for a serious condition based on early evidence suggesting clinical benefit. The indication for Alecensa is approved under accelerated approval based on tumour response rate and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ALEX is a global, randomized phase III study comparing Alecensa to crizotinib as an initial treatment for people with advanced ALK-positive NSCLC. This study is part of the company's commitment to convert the current accelerated approval in people with ALK-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib to a full approval as an initial treatment.

Alecensa is a highly selective ALK inhibitor created by Chugai. It has been reported that 2 to 5 percent of patients with NSCLC express a chromosomal rearrangement which leads to fusion of the ALK gene with another gene[1]. ALK kinase signaling is constantly active in cells with such fusion genes, resulting in uncontrolled growth of tumor cells and transforming the cells into tumor cells[2, 3]. Alecensa exerts its anti-tumor effect by selectively inhibiting ALK kinase activity to inhibit tumor cell proliferation and induce cell death[4]. In addition, Alecensa is not recognized by the transporter proteins in the blood brain barrier that actively pump molecules out of the brain. Alectinib is active in the central nervous system and has proven activity against brain metastases.

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In Europe, Roche filed the NDA to the European Medicines Agency for the approval of "*ALK* fusion gene positive unresectable, recurrent/advanced NSCLC" in September 2015. Chugai has out-licensed the rights of Alecensa to Roche in overseas countries including Europe and the US.

In Japan, Alecensa capsule 20mg, 40mg and 150mg is available to patients with "*ALK* fusion gene positive unresectable, recurrent/advanced NSCLC" and is marketed by Chugai.

1) Biomarker committee of The Japan Lung Cancer Society, Guidelines for ALK gene tests in lung cancer patients
2) Soda et al., Nature. 448: 561-566 (2007)
3) Takeuchi et al., Clin Cancer Res. 15: 3143-3149 (2009)
4) Sakamoto et al., Cancer Cell. 19: 679-690 (2011)

Overview of two pivotal clinical phase I/II trials based on the U.S. approval

- The NP28761 study is a phase I/II North American, single arm, open-label, multicentre trial evaluating the safety and efficacy of Alecensa in 87 people with ALK positive NSCLC whose disease progressed on crizotinib. (Data cut-off: October 24, 2014)
- The NP28673 study is a phase I/II global, single arm, open-label, multicentre trial evaluating the safety and efficacy of Alecensa in 138 people with ALK positive NSCLC whose disease progressed on crizotinib. (Data cut-off: primary data cut-off including safety: August 18, 2014, updated IRC data cut-off: January 8, 2015)
- People in the phase II studies received 600 mg of Alecensa orally twice daily. In both trials, the primary endpoint was ORR according to Response Evaluation Criteria in Solid Tumours (RECIST v1.1), and evaluated by an Independent Review Committee (IRC). Secondary endpoints included DOR and efficacy against disease that had spread to the CNS (CNS ORR and CNS DOR).

Efficacy Parameter	**The NP28761 study (N=87)**		**The NP28673 study (N=138)**	
	IRC* Assessment	Investigator Assessment	IRC* Assessment	Investigator Assessment
ORR (%) (95% CI)	38 (28, 49)	46 (35, 57)	44 (36, 53)	48 (39, 57)
Number of responders	33	40	61	66
DOR (median in months) (95% CI)	7.5 (4.9, Not Evaluable)	NE (4.9, Not Evaluable)	11.2 (9.6, Not Evaluable)	7.8 (7.4, 9.2)
CNS Efficacy (secondary endpoints, based on a pooled analysis of 51 people in Studies 1 and 2 with measurable CNS lesions at baseline according to RECIST v1.1[a])				
CNS ORR (%) (95% CI)	61 (46, 74)			
CNS complete response rate (%)	18			
CNS partial response rate (%)	43			
CNS DOR (median in months) (95% CI)	9.1 (5.8, Not Evaluable)			

*18 patients in Study 1 and 16 patients in Study 2 did not have measurable disease at baseline as per IRC assessment.

a Of 51 people in the subgroup, 35 (69 percent) had received prior brain radiation, including 25 (49 percent) who completed radiation treatment at least six months before starting treatment with Alecensa.

The most common Grade 3 or higher adverse events in the pooled analysis of both studies were an increase in muscle enzymes (creatine phosphokinase; 4.6 percent), shortness of breath (dyspnea; 3.6 percent), increased liver enzymes (aspartate transaminase; 3.6 percent, and alanine transaminase; 4.8 percent), evidence of liver dysfunction (hyperbilirubinemia; 2.4 percent), increased blood glucose (hyperglycemia; 2 percent), decreased levels of minerals (hypokalemia; 4 percent, hypophosphatemia; 2.8 percent, and hyponatremia; 2 percent), decreased red blood cells (anemia; 2 percent) and decreased white blood cells (lymphopenia; 4.6 percent).

About Chugai

Chugai Pharmaceutical is one of Japan's leading research-based pharmaceutical companies with strengths in biotechnology products. Chugai, based in Tokyo, specializes in prescription pharmaceuticals and is listed on the 1st section of the Tokyo Stock Exchange. As an important member of the Roche Group, Chugai is actively involved in R&D activities in Japan and abroad. Specifically, Chugai is working to develop innovative products which may satisfy the unmet medical needs, mainly focusing on the oncology area.

In Japan, Chugai's research facilities in Gotemba and Kamakura are collaborating to develop new pharmaceuticals and laboratories in Ukima are conducting research for technology development for industrial production. Overseas, Chugai Pharmabody Research based in Singapore is engaged in research focusing on the generation of novel antibody drugs by utilizing Chugai's proprietary innovative antibody engineering technologies. Chugai Pharma USA and Chugai Pharma Europe are engaged in clinical development activities in the United States and Europe.

The consolidated revenue in 2014 of Chugai totaled 461.1 billion yen and the operating income was 77.3 billion yen (IFRS Core basis).

Additional information is available on the internet at http://www.chugai-pharm.co.jp/english.

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