

## Translation

### Anti-Cancer Agent Xeloda<sup>®</sup> and Avastin<sup>®</sup> Obtained Approval for Additional Indication of Colorectal Cancer

September 24, 2009 (Tokyo) - Chugai Pharmaceutical Co., Ltd. [Main Office: Chuo-ku, Tokyo. President: Osamu Nagayama (hereafter "Chugai")] announced today that Chugai has obtained approval for the additional indication of its oral fluoropyrimidine (5-FU) anti-cancer agent capecitabine [Product name: "Xeloda<sup>®</sup> Tablets 300" (hereafter, "Xeloda<sup>®</sup>")], in combination with oxaliplatin, in the treatment of patients with "advanced or refractory colorectal cancer who are not candidates for curative surgery". Approval was received on September 18, 2009 from the Ministry of Health, Labour and Welfare (hereafter, "MHLW"). Chugai also obtained an approval for additional dosage and administration of its anti-VEGF human monoclonal antibody bevacizumab (genetical recombination) [Product name: "Avastin<sup>®</sup> Injection 100 mg/4 mL and 400 mg/16 mL" (hereafter, "Avastin<sup>®</sup>")]] on the same day.

The new approved combination therapy with Xeloda<sup>®</sup> and oxaliplatin (a regimen called "XELOX") is one of the standard treatments outside Japan for patients with advanced or refractory colorectal cancer considered unsuitable for the curative operation. With oral Xeloda, XELOX enables a once-every-three-week outpatient treatment, which reduces burdens associated with chemotherapy treatment for patients and healthcare providers.

Chugai submitted to MHLW the results from multiple overseas pivotal phase III studies and a domestic phase I/II study with the application for approval in February 2008. The overseas studies (NO16966 and NO16967) showed that XELOX was comparable to a current standard treatment, the combination therapy with 5-FU/LV and oxaliplatin (a regimen called "FOLFOX"), in terms of progression-free survival, overall survival and adverse event profile. NO16966 study also showed that XELOX in combination with Avastin<sup>®</sup> significantly improved progression-free survival, the primary endpoint of the study, compared with XELOX alone. The domestic phase I/II study showed that XELOX in combination with Avastin<sup>®</sup> was equally tolerated by Japanese patients compared with non-Japanese patients, with a response rate of 71.9% based on the Response Evaluation Criteria in Solid Tumors (RECIST).

Chugai positions Oncology as one of its key therapeutic areas. Through development of new treatment options, Chugai will continue its effort to contribute to cancer treatment.

**About Xeloda®**

Xeloda® was initially launched in the Japanese market as a treatment for inoperable or recurrent breast cancer in June 2003 by Chugai, and obtained additional approval for the overseas dosage and administration in breast cancer and a new indication of postoperative adjuvant chemotherapy for colon cancer on December 12, 2007.

**About Avastin®**

Avastin® was approved as a treatment for metastatic colorectal cancer in the US in February 2004 and is positioned as a standard treatment in the guidelines. In Japan, it was launched in June 2007 as a treatment for patients with advanced or recurrent colorectal cancer who are not considered suitable for a curative operation.

**About Oxaliplatin**

Oxaliplatin is globally positioned as a standard treatment for advanced or recurrent colorectal cancer and postoperative adjuvant chemotherapy for colon cancer. In Japan, it was approved in March 2005 and launched by the product name of Elplat® in April by Yakult Honsha Co. Ltd. as a treatment for patients with advanced or recurrent colorectal cancer who are not considered suitable for a curative operation. It was approved as a treatment for postoperative adjuvant chemotherapy for colon cancer in August 2009.

**About RECIST**

Response Evaluation Criteria in Solid Tumors (RECIST) are new guidelines for evaluation of the treatment efficacy of solid tumors.

## [Reference]

\* The underlined descriptions are newly added and changed.

Product name: Xeloda® 300 mg tablet

Generic name: capecitabine

Indications: Inoperable or recurrent breast cancer  
Postoperative adjuvant chemotherapy for colon cancer  
Advanced or refractory colorectal cancer not suited for the curative operation

Dosage and administration:

Regimens A or B are available for the treatment of inoperable or recurrent breast cancer. Regimen B should be employed for the treatment of colorectal cancer, while regimen C should be employed for the treatment of advanced or refractory colorectal cancer not suited for the curative operation in combination with another anticancer agent.

Regimen A:

XELODA is administered orally in the following doses, according to body surface area, twice daily within 30 minutes after morning and evening meals for 21 consecutive days, followed by a 7-day rest period. The administration is repeated with this taken as one course. The dosage should be adjusted according to the patient's condition.

Body surfacearea	Each dose
$<1.31\text{m}^2$	900 mg
$1.31\text{m}^2$ to $<1.64\text{m}^2$	1,200 mg
$1.64\text{m}^2$	1,500 mg

Regimen B:

XELODA is administered orally in the following doses, according to body surface area, twice daily within 30 minutes after morning and evening meals for 14 consecutive days, followed by a 7-day rest period. The administration is repeated with this taken as one course. Dosage should be reduced according to the patient's condition.

Body surfacearea	Each dose
$<1.33\text{m}^2$	1,500 mg
$1.33\text{m}^2$ to $<1.57\text{m}^2$	1,800 mg
$1.57\text{m}^2$ to $<1.81\text{m}^2$	2,100 mg
$1.81\text{m}^2$	2,400 mg

Regimen C:

XELODA is administered orally in the following doses, according to body surface area, twice daily within 30 minutes after morning and evening meals for 14 consecutive days, followed by a 7-day rest period. The administration is repeated with this taken as one course. Dosage should be reduced according to the patient's condition.

<u>Body surface area</u>	<u>Each dose</u>
<u>&lt;1.36m<sup>2</sup></u>	<u>1,200 mg</u>
<u>1.36m<sup>2</sup> to &lt; 1.66m<sup>2</sup></u>	<u>1,500 mg</u>
<u>1.66m<sup>2</sup> to &lt;1.96m<sup>2</sup></u>	<u>1,800 mg</u>
<u>1.96m<sup>2</sup></u>	<u>2,100 mg</u>

Drug price: JPY 354.1/Tablet

Product name: Avastin<sup>®</sup> for intravenous infusion 100mg/4mL  
Avastin<sup>®</sup> for intravenous infusion 400mg/16mL

Generic name: Bevacizumab (genetical recombination)

Effect/Efficacy: Advanced or refractory colorectal cancer who is not the candidate for the curative operation.

Dosage and administration:

The usual adult dosage of AVASTIN is 5 mg/kg (body weight) or 10 mg/kg (body weight) per intravenous infusion in combination with other anti-cancer chemotherapy. The administration interval of Avastin should be 2 weeks or longer.

The usual adult dosage of AVASTIN is 7.5 mg/kg (body weight) per intravenous infusion in combination with other anti-cancer chemotherapy. The administration interval of Avastin should be 3 weeks or longer.

Drug prices: Avastin<sup>®</sup> for intravenous infusion 100mg/4mL, JPY 49,959/vial  
Avastin<sup>®</sup> for intravenous infusion 400mg/16mL, JPY 190,253/vial

Xeloda<sup>®</sup> is a registered trademark of F. Hoffmann-La Roche Ltd. (Switzerland) and Avastin<sup>®</sup> is a registered trademark of Genentech, Inc. (USA).