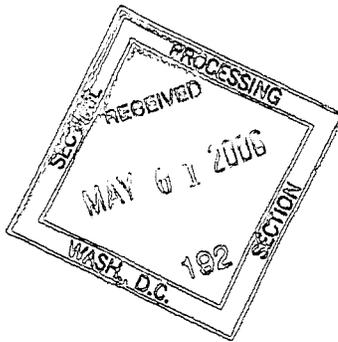


# Media release



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Basel, 28 April 2006



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## Chugai submitted Actemra in rheumatoid arthritis and a severe form of juvenile arthritis for approval in Japan PROCESSED

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Roche announced today that Chugai has filed Actemra with the Japanese Ministry of Health, Labour and Welfare (MHLW) for two additional indications: rheumatoid arthritis (RA) in adults and a devastating form of arthritis in children known as systemic onset juvenile idiopathic arthritis (sJIA). The filing follows impressive results from the Phase III programme in RA in Japan showing Actemra's use as a first line biologic and superiority over conventional disease modifying anti-rheumatic drugs (DMARDs) in monotherapy, as well as promising data in children with sJIA. Actemra is currently registered in Japan for the treatment of Castleman's disease.

"This is a significant milestone for Actemra which takes us a step closer in Japan to easing the symptoms of this debilitating disease. We look forward to the outcome of the large Phase III programme currently being conducted outside Japan where Actemra is being studied in several different patient populations of more than 4000 patients, over half of whom have already been enrolled in the various studies" commented Eduard Holdener, Head of Roche Global Pharma Development.

### Strong results in Phase III trials

Today's regulatory filing follows significant Phase III results from rheumatoid arthritis trials in Japan where Actemra monotherapy proved to be more efficacious than existing DMARDs in patients who have an inadequate response to DMARD therapy. Dramatic improvement of signs and symptoms of RA were achieved with American College of Rheumatology (ACR<sup>1</sup>) scores in the Prevention of Joint Damage (PJD) study – percentages of Actemra patients achieving ACR<sub>20</sub>, 50 and 70 were 89%, 70% and 47% compared to 35%, 14% and 6% respectively in the DMARDs group as well as in the Signs and Symptoms (S&S) study – percentage of Actemra patients achieving ACR<sub>20</sub>, 50 and 70 were 80%, 49% and 29% compared to 25%, 11% and 6% respectively in the

control arm. Furthermore, patients receiving Actemra in the PJD study showed significantly less radiographic joint destruction compared to patients in the DMARDs control group (p=0.001). Actemra has been shown to be generally well tolerated. New results from a Phase III study conducted in Japan in sJIA patients will support the filing submission for this pediatric indication. This data has been submitted for presentation at an upcoming international medical meeting.

#### About Actemra

Actemra (tocilizumab) is a new humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody whose novel mechanism of action provides a new and effective form of treatment for RA. It aims to become a major new therapeutic option for the treatment of RA, a disease with a high unmet medical need. Roche and Chugai have initiated a collaborative phase III clinical development programme in RA which is underway outside Japan with more than 4000 patients expected to be enrolled in 41 countries including several European countries and the USA.

#### About rheumatoid arthritis

Rheumatoid arthritis is a progressive, systemic autoimmune disease characterized by inflammation of the membrane lining in joints. This inflammation causes a loss of joint shape and function, resulting in pain, stiffness and swelling, ultimately leading to irreversible joint destruction and disability. Characteristics of RA include redness, swelling, pain, and movement limitation around joints of the hands, feet, elbows, knees and neck leading to loss of function. RA may also shorten life expectancy by affecting major organ systems and after 10 years, less than 50% of patients can continue to work or function normally on a day to day basis. RA affects more than 21 million people worldwide with approximately 2 million people affected in Europe. In Japan it is estimated that approximately 330,000 patients are treated for rheumatoid arthritis.

#### About systemic juvenile idiopathic arthritis

Systemic onset juvenile idiopathic arthritis (sJIA) is a severe disorder, which can have a devastating effect on children, sometimes progressing to a fatal disease. Elevated serum IL-6 is thought to play an important role in the clinical signs and symptoms of this disease. sJIA occurs in about 10% to 20% of children with juvenile inflammatory arthritis, with a prevalence of approximately 16 per 100,000 children.

#### About Roche

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#### Further information

- Chugai Pharmaceutical Co.: [www.chugai-pharm.co.jp](http://www.chugai-pharm.co.jp)

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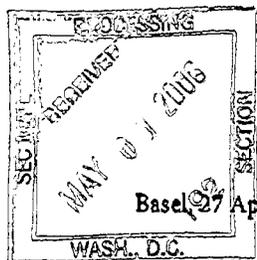
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#### References:

<sup>1</sup>The ACR response is a standard assessment used to measure patients' responses to anti-rheumatic therapies, devised by the American College of Rheumatology (ACR). It requires a patient to have a defined percentage reduction in a number of symptoms and measures of their disease. For example, a 20 or 50% level of reduction (the percentage of reduction of RA symptoms) is represented as ACR20, ACR50 or ACR70. An ACR70 response is exceptional for existing treatments and represents a significant improvement in a patient's condition.

## Media Release



### Roche submits European marketing application for novel anaemia drug CERA

**New monthly therapy advances renal anaemia management beyond capabilities of existing drugs\***

Roche, a world leader in biotechnology, today announced it has submitted a marketing authorization application to the European Medicines Agency for its novel treatment of anaemia associated with chronic kidney disease (CKD). The application, which follows the filing in the United States on April 19, includes both patients on dialysis and not on dialysis.

Roche's innovative investigational anti-anaemia agent is the first CERA, a continuous erythropoietin receptor activator which is a new class of drugs. Its activity at receptor sites involved in stimulating red blood cell production is different from that observed with traditional epoetin drugs. The distinct molecular interaction of this CERA is believed to play an important role in providing targeted, stable and sustained control of anaemia. This CERA is the only anti-anaemia treatment to have been studied with long dosing intervals of up to once monthly for its initial filing.

"At the outset we made a strategic decision at Roche to study longer dosing intervals with our CERA recognizing that the needs of physicians and patients were changing," said Eduard Holdener, Global Head Pharmaceutical Development, Roche. "With the long half-life that it naturally has, we can achieve a more predictable and sustained control of patient's haemoglobin as well as potentially offering treatment efficiencies with less frequent dosing."

With approximately one person in 10 in the general population having some degree of CKD<sup>1</sup>, it is considered a rising global epidemic and is linked to two of the fastest-growing diseases – diabetes and cardiovascular disease. Renal anaemia is a common complication of CKD that impacts morbidity, mortality and quality of life. Maintaining haemoglobin levels -- a key indicator of anaemia -- within guideline ranges is central to managing this condition. Renal anaemia remains a

major challenge as nearly 60 percent of people on dialysis who are currently being treated for it have Hb levels that aren't within accepted ranges.<sup>2</sup>

The largest and most comprehensive Phase III program ever was launched in 2004 with the objective of establishing the efficacy and safety profile of this CERA in CKD patients. In total, six different studies focussing on treatment (correction) of anaemia and maintenance (conversion from an existing therapy) were conducted in 29 countries across the globe involving more than 2,400 patients.

Using state-of-the-art protocol design and rigorous statistical testing, these six studies provided an opportunity to evaluate the efficacy and safety of CERA at extended intervals (once every two weeks in correction and up to once every four weeks in maintenance) in CKD patients on dialysis and not on dialysis and also in erythropoietin-stimulating agent (ESA)-naïve patients and previously treated patients using all approved and available ESAs as comparators. All six phase III trials were successfully completed and met their primary endpoints.

#### About Renal Anaemia

Anaemia is a condition characterized by a lower than normal level of red blood cells or the haemoglobin in them. Haemoglobin enables red blood cells to carry oxygen throughout the body. When the body is starved of the oxygen it requires, extreme fatigue sets in along with dizziness, pale skin and other symptoms. Other serious clinical complications will appear as the body – in particular, the heart - works harder to compensate for the lack of oxygen.

Normally, when the body senses a decrease in available oxygen, more erythropoietin (a protein produced by the kidneys) is created. This protein stimulates the production of oxygen-carrying red blood cells in the bone marrow which raises the red blood cell count. When this natural mechanism is hindered (as in patients with kidney disease), it is necessary to stimulate the receptors to produce red blood cells which is what CERA is designed to do. The goal of treatment is to increase haemoglobin back to a desirable level and maintain that level over time.

#### About Roche

Headquartered in Basel, Switzerland, Roche is one of the world's leading research-focused healthcare groups in the fields of pharmaceuticals and diagnostics. As a supplier of innovative products and services for the early detection, prevention, diagnosis and treatment of disease, the Group contributes on a broad range of fronts to improving people's health and quality of life. Roche is a world leader in diagnostics, the leading supplier of medicines for cancer and

transplantation and a market leader in virology. In 2005 sales by the Pharmaceuticals Division totalled 27.3 billion Swiss francs, and the Diagnostics Division posted sales of 8.2 billion Swiss francs. Roche employs roughly 70,000 people in 150 countries and has R&D agreements and strategic alliances with numerous partners, including majority ownership interests in Genentech and Chugai. Additional information about the Roche Group is available on the Internet ([www.roche.com](http://www.roche.com)).

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#### Note to Editor:

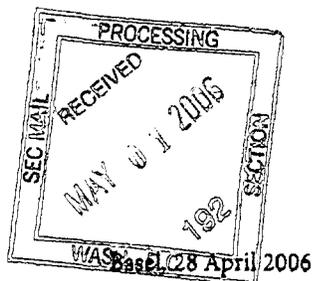
\* ESAs (Erythropoietin Stimulating Agents) is the term given for drugs that stimulate the production of red blood cells. The first ESAs on the market were recombinant human erythropoietins (referred to as rhEPOs or EPOs or epoetins) which were approved in the late 1980s or early 1990s. These short-acting drugs are generally administered three times a week to correct anaemia. There is no drug commercially available that is a pegylated epoetin. These were followed by a Novel Erythropoietin Stimulating Protein (NESP) of which there is darbepoetin alfa. This drug is given once weekly or once every two weeks to correct anaemia. The new Roche compound is the first of a new class called continuous erythropoietin receptor activator (a CERA). CERA is an acronym that describes a substance class and is not the brand name. This drug examined the correction of anaemia with a once every two-week dose interval and a once monthly dose interval for maintenance of haemoglobin in chronic kidney disease patients.

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<sup>1</sup> International Federation of Kidney Foundations fact sheet; World Kidney Day 2006. [www.ikf.net](http://www.ikf.net).

<sup>2</sup> Lascon E et al: Effect of Variability in Anemia Management on Hemoglobin Outcomes in ESRD. *Am J Kidney Dis*;41:111-124, 2003.

## Media Release



### **Herceptin receives positive opinion in Europe for early use in HER2-positive breast cancer**

**Important step towards broad access of Herceptin for women with aggressive form of breast cancer**

Roche today announced that the European Union's Committee for Human Medicinal Products (CHMP) has issued a positive recommendation for the use of Herceptin following surgery and standard chemotherapy as adjuvant treatment of early-stage HER2-positive breast cancer. HER2-positive breast cancer, which affects approximately 20% – 30%<sup>1</sup> of women with breast cancer, demands special and immediate attention because the tumours are fast-growing and there is a higher likelihood of relapse.

The CHMP's decision is based on impressive results from the international HERA (HERceptin Adjuvant) study which showed Herceptin following standard chemotherapy significantly reduces the risk of cancer coming back by 46% compared to chemotherapy alone.<sup>2</sup> These remarkable benefits have also been seen in three other major global and US studies.<sup>3</sup>

"The results from four large-scale trials speak for themselves: Herceptin consistently reduces the risk of relapse when used in early stages, providing the best chance of long-term survival to women with an extremely aggressive form of breast cancer," commented Ed Holdener, Head of Roche's Global Pharma Development. "The CHMP's timely decision represents a significant milestone, bringing patients and the medical community one step closer to broadly accessing this effective therapy in the EU."

The positive opinion will now be proposed for approval by the European Commission. Herceptin is the only approved therapy specifically for the treatment of metastatic (advanced) HER2-positive disease, so the new approval will allow Herceptin to be used following surgery for early-stage

breast cancer, as 'adjuvant' therapy.

In the US, Genentech filed a supplemental Biologic License Application (sBLA) for the use of Herceptin in early-stage HER2-positive breast cancer with the Food and Drug Administration (FDA) on February 15<sup>th</sup>, 2006. The application is based on data from the combined interim analysis of two large US trials,<sup>4</sup> and Genentech has received a priority review designation.

#### About the HERA study

HERA, conducted by the Roche and Breast International Group (BIG),<sup>5</sup> is one of the largest adjuvant studies ever carried out among breast cancer patients; enrolment to the trial began in December 2001, and nearly 5,100 HER2-positive patients were enrolled at 480 sites in 39 countries across the world. HERA is a randomised trial, which, following standard adjuvant systemic chemotherapy and radiotherapy (if applicable), evaluates observation versus Herceptin every three weeks for 12 months or 24 months in women with early-stage HER2-positive breast cancer. The HERA study allowed for the use of a wide range of chemotherapy regimens, and both lymph node-positive and lymph node-negative patients were eligible for entry into the trial.

According to the interim analysis, the primary efficacy endpoint was met, showing that in the 12-month arm, patients who received Herceptin had a statistically significant improvement in disease-free survival (the length of time after treatment during which no disease is found). At a median follow-up of one year, the secondary endpoint of overall survival had not reached statistical significance, but showed a clear trend towards an improvement in overall survival, which is to be confirmed as the data mature.

The interim analysis compared Herceptin versus observation and did not include a comparison of 12 months versus 24 months treatment duration. The trial will continue to assess this comparison and data will become available in due time as the study matures.

The HERA study has an external Independent Data Monitoring Committee (IDMC) that regularly reviews safety data. No safety concerns were raised by the IDMC, and the incidence of congestive heart failure was very low (0.5% in the Herceptin arms vs. 0% in the observation arm). Patients in this study will continue to be followed for any side effects.

### About breast cancer and Herceptin

Eight to nine percent of women will develop breast cancer during their lifetime, making it one of the most common types of cancer in women.<sup>6</sup> Each year more than one million new cases of breast cancer are diagnosed worldwide, with a death rate of nearly 400,000 people per year.

In HER2-positive breast cancer, increased quantities of the HER2 protein are present on the surface of the tumour cells. This is known as 'HER2 positivity.' High levels of HER2 are present in a particularly aggressive form of the disease which responds poorly to chemotherapy. Research shows that HER2-positivity affects approximately 20-30% of women with breast cancer.

Herceptin is a humanised antibody, designed to target and block the function of HER2, a protein produced by a specific gene with cancer-causing potential. In addition to its efficacy in the early-stage breast cancer setting, Herceptin also has demonstrated improved survival in the advanced (metastatic) setting, where its addition to chemotherapy allows patients to live up to one-third longer than chemotherapy alone.<sup>7</sup>

Herceptin received approval in the European Union in 2000 for use in patients with metastatic breast cancer, whose tumours overexpress the HER2 protein. In addition to being indicated for use in combination with docetaxel as a first-line therapy in HER2-positive patients who have not received chemotherapy for their metastatic disease, it is also indicated as a first-line therapy in combination with paclitaxel where anthracyclines are unsuitable, and as a single agent in third-line therapy. Herceptin is marketed in the United States by Genentech, in Japan by Chugai and internationally by Roche. Since 1998, Herceptin has been used to treat over 230,000 HER2-positive breast cancer patients worldwide.

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- Roche Health Kiosk on cancer: [www.health-kiosk.ch/start\\_krebs](http://www.health-kiosk.ch/start_krebs)

To access video clips, in broadcast standard, free of charge, please go to: [www.thenewsmarket.com](http://www.thenewsmarket.com).

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- <sup>1</sup> Harries M, Smith I. The development and clinical use of trastuzumab (Herceptin). *Endocr Relat Cancer* 9: 75-85, 2002.
  - <sup>2</sup> Piccart-Gebhart M, Procter M, Leyland-Jones B, et al. A Randomized Trial of Trastuzumab Following Adjuvant Chemotherapy in Women with HER2 Positive Breast Cancer. *New England Journal of Medicine* 353:16 2005.
  - <sup>3</sup> NCCTG N9831 (US), NSABP B-31 (US), BCIRG 006 (international)
  - <sup>4</sup> Romond, E., Perez, E. et al. Trastuzumab plus Adjuvant Chemotherapy for Operable HER2 Positive Breast Cancer. *New England Journal of Medicine* 353:16 2005.
  - <sup>5</sup> Collaborative partners for the HERA study include: Roche, BIG and its affiliated collaborative groups, plus non-affiliated collaborative groups, and independent sites.
  - <sup>6</sup> World Health Organization, 2000.
  - <sup>7</sup> Extra JM, Cognetti F, Maraninchi D et al. Long-term survival demonstrated with trastuzumab plus docetaxel: 24-month data from a randomised trial (M77001) in HER2-positive metastatic breast cancer. Abstract #555, American Society for Clinical Oncology (ASCO) Annual Meeting 2005.