

Basel, 4 December 2008

## **Roche and FDA Agree on Pathway Towards U.S. Approval of Actemra (tocilizumab)** Swissmedic today approved Actemra for use in Rheumatoid Arthritis

Roche today announced that the U.S. Food and Drug Administration (FDA) has provided further guidance on the requirements for the Biologics License Application (BLA) for Actemra(tocilizumab), the first interleukin-6 (IL-6) receptor-inhibiting monoclonal antibody studied for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA).

As a result of the FDA's evolving Risk Evaluation and Mitigation Strategy (REMS) requirements for medications, the Agency has clarified that a REMS plan is required to help ensure that health care professionals prescribe and administer Actemra correctly, and that patients understand the potential benefits and risks associated with this medication. Additionally, based on the evolving requirements for approval of new biologics, the FDA has asked Roche for non-clinical animal model data, beyond what was included in the Actemra BLA. Roche is performing the requested pre-clinical studies to confirm the published literature showing that Actemra does not affect peri- and post-natal development, and fertility. The FDA has not requested additional clinical studies prior to approval.

The FDA Office of Compliance has also completed its evaluation of the manufacturing facility in Japan, and has indicated that it is acceptable to manufacture Actemra.

In September, Roche received a complete response letter from the FDA for the Actemra BLA. Since then, Roche has been engaged in productive discussions with the FDA and recently met with Agency representatives for clarification on the outstanding components related to the Actemra BLA.

“Roche will continue to work diligently to fulfill the FDA's requirements, and we anticipate submitting the complete response for Actemra to the Agency in the third quarter of 2009,” said Jean-Jacques Garaud, Chief Medical Officer and Head of Global Pharma Development of Roche. “Roche remains confident in the future

of Actemra and is committed to making this important new therapy available to patients with RA.”

Roche submitted the BLA for Actemra to the FDA on November 18, 2007. The BLA for Actemra is based on the results of an extensive multi-national clinical development program, which included more than 4,000 patients in 41 countries, including the U.S. These studies demonstrated that treatment with Actemra— alone or combination with methotrexate or other DMARDs (disease modifying anti-rheumatic drugs) – significantly reduced RA signs and symptoms, regardless of previous therapy or disease severity, compared with DMARDs alone. On July 29, 2008, the Arthritis Advisory Committee of the FDA voted 10-1 to recommend approval of Actemra.

On December 3, the Swiss authorities approved RoActemra for the treatment of moderately severe to severe, active rheumatoid arthritis in adult patients who did not respond adequately to treatment with DMARDs or tumor necrosis factor (TNF) inhibitors. RoActemra can be administered as a monotherapy or in combination with methotrexate (MTX) and/or other conventional DMARDs. There are no significant Post-Approval Commitments required.

On November 21, 2008 Roche announced that the European Committee on Human Medicinal Products (CHMP) provided a positive recommendation for RoActemra (tocilizumab, known as Actemra outside the EU). This recommendation is for use of RoActemra in combination with methotrexate (MTX), for the treatment of adult patients with moderate to severe rheumatoid arthritis (RA) who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, RoActemra can be given as monotherapy in cases of intolerance to methotrexate (MTX) or where continued treatment with MTX is inappropriate.

#### **About ACTEMRA(tocilizumab)**

Actemra is the first humanized interleukin-6 (IL-6) receptor-inhibiting monoclonal antibody for RA. Studies demonstrated that reducing the activity of IL-6, one of several key cytokines involved in the inflammatory process, relieves both inflammation of the joints and certain systemic effects of RA. The extensive clinical development program conducted by Roche includes five clinical studies and has enrolled more than 4,000 patients in 41 countries, including the United States. Four Phase III studies are completed and have reported meeting their primary endpoints. The fifth Phase III study, the LITHE trial evaluating Actemra in RA is an ongoing two-year study, which is expected to report complete data evaluating the effects of Actemra on the inhibition of structural joint damage in 2009. Actemra is under review in the United States and Europe.

Actemra is part of a co-development agreement with Chugai Pharmaceuticals Co. In June 2005, Actemra was launched by Chugai in Japan as a therapy for Castleman's disease; in April 2008, additional indications for rheumatoid arthritis, juvenile idiopathic arthritis and systemic-onset juvenile idiopathic arthritis were also approved in Japan.

The serious adverse reactions reported in Actemra clinical studies include serious infections, gastrointestinal perforations and hypersensitivity reactions including anaphylaxis. The most common adverse reactions reported in clinical studies were upper respiratory tract infection, nasopharyngitis, headache, hypertension and increased ALT. Increases in liver enzymes (ALT and AST) were seen in some patients; these increases were generally mild and reversible, with no evidence of hepatic injuries. Laboratory changes, including increases in lipids (total cholesterol, LDL, HDL, triglycerides) and decreases in neutrophils and platelets, were seen in some patients without association with clinical outcomes. Treatments that suppress the immune system, such as Actemra, may cause an increase in the risk of malignancies.

#### **About IL-6**

IL-6 is a common protein found in all joints in the body and is a natural substance that can raise inflammation. Everyone has IL-6 in their body, but people with RA may have too much. When approved, Actemra will be the first and only medication to specifically target IL-6 in patients with RA.

#### **About Rheumatoid Arthritis**

Rheumatoid arthritis is a progressive, systemic autoimmune disease characterized by inflammation of the membrane lining in the 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 that leads to loss of function. In addition, the systemic symptoms of RA include fatigue, decreased hemoglobin, osteoporosis and may contribute to shortening life expectancy by affecting major organ systems. After 10 years, less than 50 percent of patients can continue to work or function normally on a daily basis. RA affects more than 21 million people worldwide with approximately 1.3 million adults affected in the United States.

#### **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 the world's biggest biotech company and an innovator of

products and services for the early detection, prevention, diagnosis and treatment of diseases, the Group contributes on a broad range of fronts to improving people's health and quality of life. Roche is the world leader in in-vitro diagnostics and drugs for cancer and transplantation, and is a market leader in virology. It is also active in other major therapeutic areas such as autoimmune diseases, inflammatory and metabolic disorders and diseases of the central nervous system. In 2007 sales by the Pharmaceuticals Division totalled 36.8 billion Swiss francs, and the Diagnostics Division posted sales of 9.3 billion francs. Roche has R&D agreements and strategic alliances with numerous partners, including majority ownership interests in Genentech and Chugai, and invested over 8 billion Swiss francs in R&D in 2007. Worldwide, the Group employs about 80,000 people. Additional information is available on the Internet at [www.roche.com](http://www.roche.com).

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