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FDA Approves ACTEMRA for the Treatment of Systemic Juvenile Idiopathic Arthritis (SJIA)

Medicine offers a new option for children living with a rare and severe form of arthritis

Roche today announced that the United States (U.S.) Food and Drug Administration (FDA) approved ACTEMRA for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients two years of age and older. ACTEMRA can be given alone or in combination with methotrexate in patients with SJIA.

ACTEMRA (tocilizumab, known as ROACTEMRA in the European Union) is the first medicine approved by the FDA for the treatment of SJIA, a rare and severe form of arthritis affecting children. SJIA has the worst long-term prognosis of all types of childhood arthritis.

"Today's FDA approval marks an important advance in the treatment of SJIA, a debilitating condition affecting children," said Hal Barron, M.D., Chief Medical Officer and Head Global Product Development. "As the first and only approved treatment for SJIA, ACTEMRA offers a new option for this extremely difficult to treat disease. This approval also demonstrates our commitment to science and patients with high unmet medical need, including orphan diseases."

SJIA is the rarest form of Juvenile Idiopathic Arthritis (JIA), also known as Juvenile Rheumatoid Arthritis (JRA).ⁱ The disease affects about 10 to 20 percent of children with JIA,ⁱⁱ with the peak age of onset between 18 months and two years,ⁱⁱⁱ although the disease can persist into adulthood. SJIA has a two to four percent overall estimated mortality rate, and accounts for almost two-thirds of all deaths among children with arthritis.^{iv} The severity of SJIA varies from person to person and can include symptoms ranging from joint inflammation accompanied by intermittent fever, skin rash, anaemia, enlargement of the liver or spleen and inflammation of the lining of the heart and/or lungs.^v In the most severe cases of SJIA, up to two-thirds of children experience chronic arthritis, and approximately half of children will develop significant joint disabilities.^{vi,vii}

About the TENDER Study

This approval was based on positive data from a Phase III study known as TENDER. The results showed that 85 percent (64/75) of children with SJIA receiving ACTEMRA experienced a 30 percent improvement (JIA ACR30) in the signs and symptoms of SJIA

and an absence of fever after 12 weeks of therapy, compared with 24 percent (9/37) of children receiving placebo (p<0.0001).^{viii}

Additional results from the TENDER study, a randomized, double-blind, Phase III study in 112 patients showed significantly more children who received ACTEMRA had improvements in SJIA signs and symptoms. In the study, 71 percent (53/75) of children treated with ACTEMRA achieved a JIA ACR70 response at week 12 compared with eight percent (3/37) of those receiving placebo (p<0.0001)

No new or unexpected safety signals were identified with ACTEMRA. The most common adverse events (at least five percent) seen in ACTEMRA treated patients in the 12 week controlled portion of the study were upper respiratory tract infection, headache, nasopharyngitis and diarrhea. The most commonly reported serious infections included pneumonia, gastroenteritis, varicella (chickenpox) and otitis media (ear infection). Sixteen percent of patients in the ACTEMRA treatment group and five percent of patients in the placebo group experienced an infusion reaction. Anaphylaxis was reported in one of the 112 patients treated with ACTEMRA during the controlled and open-label extension study.

These safety findings were consistent with results observed in the Japanese sJIA clinical program (including 149 patients treated with ACTEMRA for more than two years on average) which were included in this filing as supportive data.

This Phase III international study included 43 sites in 17 countries. The study evaluated the efficacy and safety profile of ACTEMRA versus placebo over 12 weeks in 112 children with SJIA. This study is the first part of a five-year ongoing study.

Patients two to 17 years of age with active SJIA for at least six months (average disease duration in the study was five years) who could not tolerate, or did not respond well to their current therapy (NSAIDs and systemic corticosteroids) were randomized to receive ACTEMRA (8 mg/kg if weight \geq 30 kg or 12 mg/kg if weight <30 kg) or placebo every two weeks as a 60-minute single intravenous drip infusion for a total of 12 weeks. Patients continued to receive NSAIDs, corticosteroids and methotrexate if receiving these medicines at the start of the study. The primary endpoint was the number of patients treated with ACTEMRA with a JIA ACR30 response and absence of fever at week 12, compared with those receiving placebo.

About ACTEMRA[®]

ACTEMRA is the result of research collaboration by Chugai and is also being co-developed globally with Chugai. ACTEMRA is the first humanised interleukin-6 (IL-6) receptor-inhibiting monoclonal antibody. ACTEMRA was first approved in Japan, and launched by Chugai in June 2005 as a therapy for Castleman's disease; in April 2008, additional indications for rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis and systemic-onset juvenile idiopathic arthritis were also approved in Japan. ACTEMRA was approved in the European Union in January 2009 for the treatment of RA in patients 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) inhibitors. It is also approved for use in over 90 other countries, including India, Brazil, Switzerland, and Australia. ACTEMRA was approved in the

United States in January 2010 for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more TNF inhibitors. In addition, ACTEMRA is now approved in the United States for the treatment of active SJIA in patients two years of age and older.

The safety and efficacy of ACTEMRA in RA has been established in an extensive clinical development program including five Phase III clinical studies that enrolled more than 4,000 people with RA in 41 countries, including the United States. The overall safety profile of ACTEMRA/RoACTEMRA is consistent across all global clinical studies. The serious adverse events reported in ACTEMRA/RoACTEMRA clinical studies include serious infections, gastrointestinal perforations and hypersensitivity reactions including anaphylaxis. The most common adverse events 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 or any observed impact on liver function. 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/RoACTEMRA, may cause an increase in the risk of malignancies.

About Roche

Headquartered in Basel, Switzerland, Roche is a leader in research-focused healthcare with combined strengths in pharmaceuticals and diagnostics. Roche is the world's largest biotech company with truly differentiated medicines in oncology, virology, inflammation, metabolism and CNS. Roche is also the world leader in in-vitro diagnostics, tissue-based cancer diagnostics and a pioneer in diabetes management. Roche's personalised healthcare strategy aims at providing medicines and diagnostic tools that enable tangible improvements in the health, quality of life and survival of patients. In 2010, Roche had over 80,000 employees worldwide and invested over 9 billion Swiss francs in R&D. The Group posted sales of 47.5 billion Swiss francs. Genentech, United States, is a wholly owned member of the Roche Group. Roche has a majority stake in Chugai Pharmaceutical, Japan. For more information: www.roche.com.

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