Hypersensitivity reactions, including anaphylaxis: Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA and anaphylactic events with a fatal outcome have been reported with intravenous infusion of ACTEMRA.

Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials of intravenous ACTEMRA, 0.2% (8 out of 4009) of patients in the intravenous all-exposure rheumatoid arthritis population, 0.7 % (8 out of 1068) in the SC 6-month controlled RA trials, and in 0.7% (10 out of 1465) of patients in the SC all-exposure population.

In the SJIA controlled trial with intravenous ACTEMRA, 1 out of 112 patients (0.9%) experienced hypersensitivity reaction that required treatment discontinuation. In the PJIA controlled trial with intravenous ACTEMRA, 0 out of 188 patients (0%) in the ACTEMRA all-exposure population experienced hypersensitivity reactions that required treatment discontinuation. Reactions that required treatment discontinuation included generalized erythema, rash and urticaria. Injection site reactions were categorized separately.

In the postmarketing setting, events of hypersensitivity reactions, including anaphylaxis and death have occurred in patients treated with a range of doses of intravenous ACTEMRA, with or without concomitant arthritis therapies. Events have occurred in patients who received premedication. Hypersensitivity, including anaphylaxis events, have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA.

ACTEMRA for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. For ACTEMRA subcutaneous injection, advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of ACTEMRA immediately and discontinue ACTEMRA permanently. Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA.

Please see the Prescribing Information for more information.

Reporting Adverse Events

It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you provide about these events may inform therapy and monitoring decisions for future patients.

Reporting maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting*. You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-888-835-2555

- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for Prescribing Information and Medication Guide.

ATTACHMENT D: JOURNAL INFORMATION PIECE FOR GASTROENTEROLOGISTS AND HEPATOLOGISTS

Important Safety Information for Gastroenterologists and Hepatologists About Potential Risks of Gastrointestinal Perforation and Transaminase Elevations With ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist that has been approved by the Food and Drug Administration (FDA) for three indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs) with a recommended ACTEMRA dosing interval of every 4 weeks for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.

- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA dosing interval of every 4 weeks for IV administration.

- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA dosing interval of every 2 weeks for IV administration.

The safety and efficacy of ACTEMRA for conditions other than RA, PJIA and SJIA have not yet been established.

Gastroenterologists and **hepatologists** should be aware of important safety information regarding ACTEMRA.

Gastrointestinal perforations: Gastrointestinal (GI) perforations have been reported in Phase 3 clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

Transaminase elevations: Treatment with ACTEMRA was associated with a higher incidence of transaminase elevations (ALT, AST) in Phase 3 clinical trials. These elevations did not result in apparent permanent or clinically evident hepatic injury with modification of the treatment regimen, which resulted in a decrease or normalization of liver enzymes. Monitor patients receiving ACTEMRA for elevated transaminase levels; dose modifications may be necessary. When clinically indicated, consider other liver function tests, such as bilirubin.

Please see the Prescribing Information for more information.

Reporting Adverse Events
It is important that you report any serious gastrointestinal adverse events, including GI perforation, hepatic disease or hepatic impairment, that occur in a patient being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you, as a gastroenterologist or hepatologist, provide about these events may inform therapy and monitoring decisions for future patients.

Reporting maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting*. You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-888-835-2555
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

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ATTACHMENT E: JOURNAL INFORMATION PIECE FOR INFECTIOUS DISEASE SPECIALISTS

Important Safety Information for Infectious Disease Specialists About Potential Risks of Infections With ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist that has been approved by the Food and Drug Administration (FDA) for three indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs) with a recommended ACTEMRA dosing interval of every 4 weeks for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.

- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA dosing interval of every 4 weeks for IV administration.

- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA dosing interval of every 2 weeks for IV administration.

The safety and efficacy of ACTEMRA® for conditions other than RA, PJIA and SJIA have not yet been established.

Infectious disease specialists should be aware of important safety information regarding ACTEMRA.

Serious infections: Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections.

Avoid ACTEMRA during an active infection, including localized infections. If a serious infection develops, hold ACTEMRA until the infection is controlled.

Reporting Adverse Events

It is important that you report all serious infections that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you, as an infectious disease specialist, provide about these events may inform therapy and monitoring decisions for future patients.

Reporting maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting*. You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-888-835-2555
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

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ATTACHMENT F: JOURNAL INFORMATION PIECE FOR INTERNISTS AND INTERNAL MEDICINE SUBSPECIALISTS

Important Safety Information for Physicians About Risks in Patients Receiving ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist that has been approved by the Food and Drug Administration (FDA) for three indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs) with a recommended ACTEMRA dosing interval of every 4 weeks for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.

- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA dosing interval of every 4 weeks for IV administration.

- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA dosing interval of every 2 weeks for IV administration.

The safety and efficacy of ACTEMRA for conditions other than RA, PJIA and SJIA have not yet been established.

Physicians should be aware of important information regarding safety and laboratory monitoring recommendations for ACTEMRA.

Serious infections: Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections**.**

Gastrointestinal perforations: Gastrointestinal (GI) perforations have been reported in Phase 3 clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

Hypersensitivity reactions, including anaphylaxis:
Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA and anaphylactic events with a fatal outcome have been reported with intravenous infusion of ACTEMRA.

Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials of intravenous ACTEMRA, 0.2% (8 out of 4009) of patients in the

intravenous all-exposure rheumatoid arthritis population, 0.7 % (8 out of 1068) in the SC 6-month controlled RA trials, and in 0.7% (10 out of 1465) of patients in the SC all-exposure population.

In the SJIA controlled trial with intravenous ACTEMRA, 1 out of 112 patients (0.9%) experienced hypersensitivity reaction that required treatment discontinuation. In the PJIA controlled trial with intravenous ACTEMRA, 0 out of 188 patients (0%) in the ACTEMRA all-exposure population experienced hypersensitivity reactions that required treatment discontinuation. Reactions that required treatment discontinuation included generalized erythema, rash and urticaria. Injection site reactions were categorized separately.

In the postmarketing setting, events of hypersensitivity reactions, including anaphylaxis and death have occurred in patients treated with a range of doses of intravenous ACTEMRA, with or without concomitant arthritis therapies. Events have occurred in patients who received premedication. Hypersensitivity, including anaphylaxis events, have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA.

ACTEMRA for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. For ACTEMRA subcutaneous injection, advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of ACTEMRA immediately and discontinue ACTEMRA permanently. Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA.

Please see the Prescribing Information for more information.

Demyelinating disorders: The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies of adults with RA. Monitor patients for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

Malignancies: Malignancies were observed in clinical studies of ACTEMRA. The impact of treatment with ACTEMRA on the development of the malignancies is not known, but malignancy is a known risk of biological products that suppress the immune system. ACTEMRA is an immunosuppressant and may increase the risk of malignancies.

Laboratory abnormalities: Hepatic transaminases (ALT, AST), lipids, neutrophils, and platelets should be monitored, as abnormalities in these parameters were associated with ACTEMRA treatment in Phase 3 clinical trials. Dosage modifications may be required if laboratory abnormalities occur.

Please see the Prescribing Information for more information.

Reporting Adverse Events
It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. As an ACTEMRA-prescribing internist and/or internal medicine subspecialist, such as a rheumatologist, the information you provide about these events may inform therapy and monitoring decisions for future patients.

Reporting maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting*. You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-888-835-2555
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

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ATTACHMENT G: JOURNAL INFORMATION PIECE FOR NEUROLOGISTS

Important Safety Information for Neurologists About Demyelinating Disorders in Co-managing Rheumatoid Arthritis Patients Receiving ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist that has been approved by the Food and Drug Administration (FDA) for three indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs) with a recommended ACTEMRA dosing interval of every 4 weeks for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.

- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA dosing interval of every 4 weeks for IV administration.

- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA dosing interval of every 2 weeks for IV administration.

The safety and efficacy of ACTEMRA for conditions other than RA, PJIA and SJIA have not yet been established.

Neurologists co-managing RA patients should be aware of important safety information regarding treatment with ACTEMRA.

Demyelinating disorders: The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies of adults with RA. Monitor patients for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

Reporting Adverse Events
It is important that you report any serious neurologic adverse event, including demyelinating disorders, that occurs in a patient being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you, as a neurologist, provide about these events may inform therapy and monitoring decisions for future patients.

Reporting and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting*. You can report your cases to Genentech or directly to the FDA:
- Genentech at 1-888-835-2555
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

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ATTACHMENT H: JOURNAL INFORMATION PIECE FOR ONCOLOGISTS

Important Safety Information for Oncologists
About Malignancy Risk With ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist that has been approved by the Food and Drug Administration (FDA) for three indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs) with a recommended ACTEMRA dosing interval of every 4 weeks for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.

- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA® dosing interval of every 4 weeks for IV administration.

- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks for IV administration.

The safety and efficacy of ACTEMRA for conditions other than RA, PJIA and SJIA have not yet been established.

Oncologists should be aware of important safety information about ACTEMRA.

Malignancies were observed in clinical studies of ACTEMRA. The impact of treatment with ACTEMRA on the development of the malignancies is not known, but malignancy is a known risk of biological products that suppress the immune system. ACTEMRA is an immunosuppressant and may increase the risk of malignancies.

Reporting Adverse Events
If you are consulted to a see a patient with cancer at any time after receiving ACTEMRA therapy, it is important that you report the case, even if you do not think there is a causal relationship. The information that you, as an oncologist, provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting*. You can report your cases to Genentech or directly to the FDA:
- Genentech at 1-888-835-2555
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

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ATTACHMENT I: JOURNAL INFORMATION PIECE FOR RHEUMATOLOGISTS

Important Safety Information for Rheumatologists About Risks in Patients Receiving ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist that has been approved by the Food and Drug Administration (FDA) for three indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs) with a recommended ACTEMRA dosing interval of every 4 weeks for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.

- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA dosing interval of every 4 weeks for IV administration.

- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA dosing interval of every 2 weeks for IV administration.

The safety and efficacy of ACTEMRA for conditions other than RA, PJIA and SJIA have not yet been established.

Rheumatologists should be aware of important information regarding safety and laboratory monitoring recommendations for ACTEMRA.

Serious infections: Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections.

Gastrointestinal perforations: Gastrointestinal (GI) perforation have been reported in Phase 3 clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

Hypersensitivity Reactions, Including Anaphylaxis
Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA and anaphylactic events with a fatal outcome have been reported with intravenous infusion of ACTEMRA.

Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials, and in 0.2% (8 out of 4009) of patients in the intravenous all-exposure rheumatoid arthritis population, 0.7 % (8 out of 1068) in the SC 6-month

It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. As an ACTEMRA-prescribing rheumatologist, the information you provide about these events may inform therapy and monitoring decisions for future patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting*. You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-888-835-2555
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

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