ATTACHMENT B: PRESCRIBER EDUCATION SLIDE DECK
ACTEMRA Risk Mitigation Strategy

Presenter Name, Degree
Medical Science Liaison
Genentech, Inc.

Version: 10/2013
**Indications and Dosage**

*Rheumatoid Arthritis (RA) (1 of 2)*

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### Indication in RA

- ACTEMRA (tocilizumab) is indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

### Dosage in RA

- ACTEMRA may be used as monotherapy or concomitantly with methotrexate or other non-biologic DMARDs.

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ACTEMRA Prescribing Information, 10/2013
## Indications and Dosage

*Rheumatoid Arthritis (RA) (2 of 2)*

### Recommended Intravenous (IV) Dosage Regimen in RA

- The recommended dosage of ACTEMRA for adult patients given as a 60-minute single IV drip infusion is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.
- Doses exceeding 800 mg per infusion are not recommended in RA patients.

### Recommended Subcutaneous (SC) Dosage Regimen in RA

<table>
<thead>
<tr>
<th>Patients less than 100 kg weight</th>
<th>162 mg administered SC every other week, followed by an increase to every week based on clinical response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at or above 100 kg weight</td>
<td>162 mg administered SC every week</td>
</tr>
</tbody>
</table>

- When transitioning from ACTEMRA IV therapy to SC administration, administer the first SC dose instead of the next scheduled IV dose.
Indications and Dosage
Polyarticular Juvenile Idiopathic Arthritis (PJIA)

Indication in PJIA
- ACTEMRA (tocilizumab) is indicated for the treatment of active PJIA in patients 2 years of age and older.

Dosage in PJIA
- ACTEMRA may be used alone or in combination with methotrexate.

Recommended IV PJIA Dosage Every 4 Weeks (as a 60-minute single IV drip infusion)

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients less than 30 kg</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>Patients at or above 30 kg</td>
<td>8 mg/kg</td>
</tr>
</tbody>
</table>

- SC administration is not approved for PJIA.

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### Indications and Dosage

**Systemic Juvenile Idiopathic Arthritis (SJIA)**

#### Indication in SJIA

- ACTEMRA (tocilizumab) is indicated for the treatment of active SJIA in patients 2 years of age and older.

#### Dosage in SJIA

- ACTEMRA may be used alone or in combination with methotrexate.

#### Recommended IV SJIA Dosage Every 2 Weeks

(as a 60-minute single IV drip infusion)

<table>
<thead>
<tr>
<th>Weight Condition</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients less than 30 kg weight</td>
<td>12 mg/kg</td>
</tr>
<tr>
<td>Patients at or above 30 kg weight</td>
<td>8 mg/kg</td>
</tr>
</tbody>
</table>

- SC administration is not approved for SJIA.
Overview of Adverse Events of Special Interest

- Serious Infections
- Gastrointestinal Perforations
- Laboratory Parameters
  - Low absolute neutrophil count
  - Reduction in platelet count
  - Elevations in liver function tests
  - Increases in lipid parameters
- Immunosuppression and Malignancies
- Hypersensitivity Reactions, Including Anaphylaxis
- Demyelinating Disorders
Boxed Warning
Serious Infections

Do not administer ACTEMRA in patients with an active infection, including localized infections.

Important Information

- Patients treated with ACTEMRA are at increased risk for developing serious infections that may lead to hospitalization or death.
- Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Recommendation in RA, PJIA, and SJIA

- If a serious infection develops, interrupt ACTEMRA until infection is controlled.
- The risks and benefits of treatment with ACTEMRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.
- Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ACTEMRA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.
Warnings and Precautions
Gastrointestinal Perforations

Important Information
• Events of gastrointestinal perforation have been reported in clinical trials, primarily as complications of diverticulitis in RA patients.

Recommendation in RA, PJIA, and SJIA
• Use ACTEMRA with caution in patients who may be at increased risk for gastrointestinal perforation.
• Promptly evaluate patients presenting with new onset abdominal symptoms for early identification of gastrointestinal perforation.

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## Warnings and Precautions

### Laboratory Parameters: Neutropenia

**Important Information**

- Treatment with ACTEMRA was associated with a higher incidence of neutropenia.
- Infections have been uncommonly reported in association with treatment-related neutropenia in long-term extension studies and postmarketing clinical experience.

<table>
<thead>
<tr>
<th>Recommendation in RA</th>
<th>Recommendation in PJIA</th>
<th>Recommendation in SJIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• It is NOT recommended to initiate ACTEMRA treatment in patients with an absolute neutrophil count (ANC) below 2000 per mm³.</td>
<td>• It is NOT recommended to initiate ACTEMRA treatment in patients with an absolute neutrophil count (ANC) below 2000 per mm³.</td>
<td>• It is NOT recommended to initiate ACTEMRA treatment in patients with an absolute neutrophil count (ANC) below 2000 per mm³.</td>
</tr>
<tr>
<td>• Monitor neutrophils 4 to 8 weeks after start of therapy and every 3 months thereafter.</td>
<td>• Monitor neutrophils at the <strong>time of the second infusion and thereafter every 4 to 8 weeks.</strong></td>
<td>• Monitor neutrophils at the <strong>time of the second infusion and thereafter every 2 to 4 weeks.</strong></td>
</tr>
</tbody>
</table>
### Dosage Modifications

**Low Absolute Neutrophil Count (ANC)**

<table>
<thead>
<tr>
<th>ANC (cells/mm³)</th>
<th>Recommendation in RA</th>
<th>Recommendation in PJIA and SJIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1000</td>
<td>- Maintain ACTEMRA dose</td>
<td>- Maintain ACTEMRA dose</td>
</tr>
<tr>
<td></td>
<td>- Hold ACTEMRA dosing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- When ANC greater than 1000 cells per mm³:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- For patients receiving IV ACTEMRA, resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg as clinically appropriate.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- For patients receiving SC ACTEMRA, resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate.</td>
<td></td>
</tr>
<tr>
<td>500-1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Discontinue ACTEMRA</td>
<td>The decision to discontinue ACTEMRA for a laboratory abnormality should be based on the medical assessment of the individual patient.</td>
</tr>
<tr>
<td>&lt;500</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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## Warnings and Precautions

*Laboratory Parameters: Thrombocytopenia*

### Important Information

- Treatment with ACTEMRA was associated with a reduction in platelet counts.
- Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials.

<table>
<thead>
<tr>
<th>Recommendation in RA</th>
<th>Recommendation in PJIA</th>
<th>Recommendation in SJIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is <strong>NOT</strong> recommended to initiate ACTEMRA treatment in patients with a platelet count &lt;100,000/mm³.</td>
<td>It is <strong>NOT</strong> recommended to initiate ACTEMRA treatment in patients with a platelet count &lt;100,000/mm³.</td>
<td>It is <strong>NOT</strong> recommended to initiate ACTEMRA treatment in patients with a platelet count &lt;100,000/mm³.</td>
</tr>
<tr>
<td>Monitor platelets 4 to 8 weeks after start of therapy and every 3 months thereafter.</td>
<td>Monitor platelets at the time of the second infusion and thereafter every 4 to 8 weeks.</td>
<td>Monitor platelets at the time of the second infusion and thereafter every 2 to 4 weeks.</td>
</tr>
</tbody>
</table>

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# Dosage Modifications

## Low Platelet Count

<table>
<thead>
<tr>
<th>Platelet Count (cells/mm²)</th>
<th>Recommendation in RA</th>
<th>Recommendation in PJIA and SJIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>50,000 – 100,000</strong></td>
<td>• Hold ACTEMRA dosing</td>
<td>• Dose interruptions of ACTEMRA are recommended for low platelet counts at levels similar to what is outlined for patients with RA.</td>
</tr>
<tr>
<td></td>
<td>• When platelet count is greater than 100,000 cells per mm²:</td>
<td>• If appropriate, dose modify or stop concomitant MTX and/or other medications.</td>
</tr>
<tr>
<td></td>
<td>• For patients receiving IV ACTEMRA, resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg as clinically appropriate.</td>
<td>• Hold ACTEMRA dosing until the clinical situation has been evaluated.</td>
</tr>
<tr>
<td></td>
<td>• For patients receiving SC ACTEMRA, resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate.</td>
<td></td>
</tr>
<tr>
<td><strong>&lt;50,000</strong></td>
<td>• Discontinue ACTEMRA</td>
<td>• The decision to discontinue ACTEMRA for a laboratory abnormality should be based on the medical assessment of the individual patient.</td>
</tr>
</tbody>
</table>
## Warnings and Precautions

### Laboratory Parameters: Elevated Liver Enzymes

### Important Information
- Treatment with ACTEMRA was associated with a higher incidence of transaminase elevations.
- These elevations did not result in apparent permanent or clinically evident hepatic injury in clinical trials.
- Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with ACTEMRA.

### Recommendation in RA
- It is NOT recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST greater than 1.5 times the upper limit of normal (ULN).
- Monitor ALT and AST levels 4 to 8 weeks after start of therapy and every 3 months thereafter.
- When clinically indicated, other liver function tests such as bilirubin should be considered.

### Recommendation in PJIA
- It is NOT recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST greater than 1.5 times the upper limit of normal (ULN).
- Monitor ALT and AST at the time of the second infusion and thereafter every 4 to 8 weeks.
- When clinically indicated, other liver function tests such as bilirubin should be considered.

### Recommendation in SJIA
- It is NOT recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST greater than 1.5 times the upper limit of normal (ULN).
- Monitor ALT and AST at the time of the second infusion and thereafter every 2 to 4 weeks.
- When clinically indicated, other liver function tests such as bilirubin should be considered.

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## Dosage Modifications

### Elevated Liver Enzymes

<table>
<thead>
<tr>
<th>ALT or AST Value</th>
<th>Recommendation in RA</th>
<th>Recommendation in PJIA and SJIA</th>
</tr>
</thead>
</table>
| >1 to 3x ULN     | • Dose modify concomitant DMARDs if appropriate.  
                  • For persistent increases in this range:  
                    - For patients receiving IV ACTEMRA, reduce dose to 4 mg per kg or hold ACTEMRA until ALT or AST have normalized.  
                    - For patients receiving SC ACTEMRA, reduce injection frequency to every other week or hold dosing until ALT or AST have normalized. Resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate. | • Dose interruptions of ACTEMRA are recommended for liver enzyme abnormalities at levels similar to what is outlined for patients with RA.  
• If appropriate, dose modify or stop concomitant MTX and/or other medications.  
• Hold ACTEMRA dosing until the clinical situation has been evaluated. |
| >3 to 5x ULN (confirmed by repeating testing) | • Hold ACTEMRA dosing until less than 3x ULN and follow recommendation above for greater than 1 to 3x ULN.  
• For persistent increases greater than 3x ULN, discontinue ACTEMRA. | • Dose interruptions of ACTEMRA are recommended for liver enzyme abnormalities at levels similar to what is outlined for patients with RA.  
• If appropriate, dose modify or stop concomitant MTX and/or other medications.  
• Hold ACTEMRA dosing until the clinical situation has been evaluated. |
| >5x ULN          | • Discontinue ACTEMRA | • The decision to discontinue ACTEMRA for a laboratory abnormality should be based on the medical assessment of the individual patient. |

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**Warnings and Precautions**

*Laboratory Parameters: Lipid Abnormalities*

**Important Information**
- Treatment with ACTEMRA was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol.

**Recommendation in RA, PJIA, and SJIA**
- Assess lipid parameters approximately 4 to 8 weeks following initiation of ACTEMRA therapy, then at approximately 24 week intervals.
- Manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.
- Exercise caution when coadministering ACTEMRA with CYP3A4 substrate drugs where decrease in effectiveness is undesirable (e.g., lovastatin, atorvastatin, etc.).

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Important Information

• The impact of treatment with ACTEMRA on the development of malignancies is not known but malignancies were observed in clinical studies.
• ACTEMRA is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.
Warnings and Precautions
Hypersensitivity Reactions, Including Anaphylaxis (1 of 2)

Important Information

- Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA and anaphylactic events with a fatal outcome have been reported with IV 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 IV ACTEMRA, 0.2% (8 out of 4009) of patients in the IV all-exposure RA population, 0.7% (8 out of 1068) in the SC 6-month controlled RA trials, and in 0.7% (10 out of 1458) of patients in the SC all-exposure population.
- In the SJIA controlled trial with IV ACTEMRA, 1 out of 112 patients (0.9%) experienced hypersensitivity reactions that required treatment discontinuation.
- In the PJIA controlled trial with IV 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.
Warnings and Precautions
Hypersensitivity Reactions, Including Anaphylaxis (2 of 2)

Recommendation in RA, PJIA, and SJIA

- ACTEMRA should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis.
- If anaphylaxis or other clinically significant hypersensitivity reaction occurs, administration of ACTEMRA should be stopped immediately and ACTEMRA should be permanently discontinued.
- Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA.
- For ACTEMRA subcutaneous injection, advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction.
**Warnings and Precautions**

*Demyelinating Disorders*

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**Important Information**

- The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in RA clinical studies.

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**Recommendation in RA, PJIA, and SJIA**

- 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.

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