

Tocilizumab

Indications/Dosage

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Labeled

- cytokine release syndrome
- polyarticular juvenile idiopathic arthritis
- rheumatoid arthritis
- systemic juvenile idiopathic arthritis
- temporal arteritis

Off-Label

- coronavirus disease 2019 (COVID-19) †
- scleroderma (systemic sclerosis) †
- severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection †

† Off-label indication

For the treatment of moderately- to severely-active rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs

Intravenous dosage

- **Adults**

4 mg/kg IV infusion given over 1 hour every 4 weeks. May increase dose to 8 mg/kg IV every 4 weeks if needed; doses greater than 800 mg per infusion are not recommended. May use as monotherapy or concomitantly with methotrexate or other non-biologic DMARDs. Avoid concurrent use with biological DMARDs such as tumor necrosis factor (TNF) modifiers, anakinra, rituximab, ofatumumab, and abatacept. [\[38283\]](#)

Subcutaneous dosage

- **Adults weighing less than 100 kg**

162 mg subcutaneously every other week as monotherapy or concomitantly with methotrexate or other non-biologic DMARDs. Increase to 162 mg subcutaneously once weekly based on clinical response. If transitioning from IV tocilizumab, give the first subcutaneous dose instead of the next scheduled IV dose. [\[38283\]](#)

- **Adults weighing 100 kg or more**

162 mg subcutaneously once weekly as monotherapy or concomitantly with methotrexate or other non-biologic DMARDs. If transitioning from IV tocilizumab, give the first subcutaneous dose instead of the next scheduled IV dose. [\[38283\]](#)

INVESTIGATIONAL USE: For adjunctive use in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection†, the virus that causes coronavirus disease 2019 (COVID-19)†

Intravenous dosage

- **Adults**

Available data are limited, and efficacy has not been established. Due to a lack of clinical data, the National Institutes of Health (NIH) COVID-19 treatment guidelines do not recommend for or against the use of IL-6 receptor inhibitors, such as tocilizumab.^[65314] 4 to 8 mg/kg/dose (Usual dose: 400 mg; Max dose: 800 mg) IV once is being evaluated in combination with antiviral therapy.^[65148] ^[65162] ^[65163] ^[65191] ^[65193] ^[65194] A second dose administered 8 to 12 hours after the first infusion may be considered in patients who show a lack of clinical response (i.e., continued fever).^[65148] ^[65163] ^[65193] One protocol suggests a possible third dose administered 16 to 24 hours after the first dose.^[65148]

For the treatment of active polyarticular juvenile idiopathic arthritis

NOTE: Tocilizumab has been designated an orphan drug by the FDA for this indication.

Intravenous dosage

- **Children and Adolescents 2 to 17 years weighing 30 kg or more**

8 mg/kg/dose IV every 4 weeks; administer over 1 hour. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate. May use as monotherapy or in combination with methotrexate.^[38283]

- **Children and Adolescents 2 to 17 weighing less than 30 kg**

10 mg/kg/dose IV every 4 weeks; administer over 1 hour. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate. May use as monotherapy or in combination with methotrexate.^[38283]

Subcutaneous dosage

- **Children and Adolescents 2 to 17 years weighing 30 kg or more**

162 mg/dose subcutaneously every 2 weeks. When transitioning from IV to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled IV dose. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate. May use as monotherapy or in combination with methotrexate.^[38283]

- **Children and Adolescents 2 to 17 years weighing less than 30 kg**

162 mg/dose subcutaneously every 3 weeks. When transitioning from IV to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled IV dose. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate. May use as monotherapy or in combination with methotrexate.^[38283]

For the treatment of active systemic juvenile idiopathic arthritis

Intravenous dosage

- **Children and Adolescents 2 to 17 years weighing 30 kg or more**

8 mg/kg/dose IV every 2 weeks; administer over 1 hour. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate. May use as monotherapy or in combination with methotrexate.[38283]

- **Children and Adolescents 2 to 17 years weighing less than 30 kg**

12 mg/kg/dose IV every 2 weeks; administer over 1 hour. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate. May use as monotherapy or in combination with methotrexate.[38283]

Subcutaneous dosage

- **Children and Adolescents 2 to 17 years weighing 30 kg or more**

162 mg/dose subcutaneously every week. When transitioning from IV to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled IV dose. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate. May use as monotherapy or in combination with methotrexate.[38283]

- **Children and Adolescents 2 to 17 years weighing less than 30 kg**

162 mg/dose subcutaneously every 2 weeks. When transitioning from IV to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled IV dose. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate. May use as monotherapy or in combination with methotrexate.[38283]

For the treatment of systemic scleroderma (systemic sclerosis)†

Strength of Recommendation: Equivocal/Weak For

Level of Evidence: Very Low, [Detailed Level of Evidence](#)

NOTE: Tocilizumab has been designated an orphan drug by the FDA for this indication.

Intravenous dosage

- **Adults**

8 mg/kg IV once monthly.[62882]

Subcutaneous dosage

- **Adults**

162 mg subcutaneously once weekly.[\[62883\]](#)

For the treatment of temporal arteritis, also known as giant cell arteritis (GCA)

Subcutaneous dosage

- **Adults**

162 mg subcutaneously once weekly, in combination with a tapering course of glucocorticoids, is the recommended dose. A dose of 162 mg subcutaneously once every other week, in combination with a tapering course of glucocorticoids, may be prescribed based on clinical considerations. Tocilizumab may be used alone following discontinuation of glucocorticoids.[\[38283\]](#)

For the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS)

Intravenous dosage

- **Adults, Adolescents, and Children 2 years old and older, weighing 30 kg or more**

8 mg/kg IV over 60 minutes for one dose, alone or in combination with corticosteroids. If no clinical improvement in the signs and symptoms of CRS occur after the first dose, up to 3 additional doses of tocilizumab may be administered at least 8 hours apart; doses exceeding 800 mg are not recommended. Only the intravenous route should be used for the treatment of CRS; subcutaneous administration is not approved for this use. In a retrospective analysis of pooled outcome data from clinical trials of CAR T-cell therapies for hematologic malignancies, 69% of patients with a first episode of CRS who were treated with tocilizumab achieved a response, defined as resolution (lack of fever and off vasopressors for at least 24 hours) within 14 days of the first dose of tocilizumab, less than 2 doses of tocilizumab administered, and no additional treatment beyond tocilizumab and corticosteroids. This was confirmed in a second study using an independent cohort that included 14 patients with CAR T cell-induced CRS.[\[38283\]](#)

- **Adults, Adolescents, and Children 2 years old and older, weighing less than 30 kg**

12 mg/kg IV infusion over 60 minutes for one dose, alone or in combination with corticosteroids. If no clinical improvement in the signs and symptoms of CRS occur after the first dose, up to 3 additional doses of tocilizumab may be administered at least 8 hours apart; doses exceeding 800 mg are not recommended. Only the IV route should be used for the treatment of CRS; subcutaneous administration is not approved for this use. In a retrospective analysis of pooled outcome data from clinical trials of CAR T-cell therapies for hematologic malignancies, 69% of patients with a first episode of CRS who were treated with tocilizumab achieved a response, defined as resolution (lack of fever and off vasopressors for at least 24 hours) within 14 days of the first dose of tocilizumab, less than 2 doses of tocilizumab administered, and no additional treatment beyond tocilizumab and corticosteroids. This was confirmed in a second study using an independent cohort that included 14 patients with CAR T cell-induced CRS.[\[38283\]](#)

Therapeutic Drug Monitoring

Prior to initiation of treatment

Check the patient's ANC, platelet count, and liver function tests (ALT/AST concentrations) before tocilizumab initiation. In adults, tocilizumab is not recommended for patients with an ANC less than 2,000/mm³, a platelet count less than 100,000/mm³, or an ALT or AST greater than 1.5 times the upper limit of normal (ULN). In patients with severe or life-threatening cytokine releasing syndrome (CRS) who also have cytopenias and/or elevated hepatic enzymes due to lymphodepleting chemotherapy or the CRS, consider the potential benefit of treating the CRS versus the risks of short-term treatment with tocilizumab.[38283]

Dosage modifications for adult patients with rheumatoid arthritis or giant cell arteritis

Absolute neutrophil count (ANC) 500 to 1,000 cells/mm³: Hold tocilizumab and restart when ANC more than 1,000 cells/mm³ with IV dosing at 4 mg/kg with an increase to 8 mg/kg as clinically appropriate or subcutaneous dosing at every other week with an increase to weekly as clinically appropriate.

Absolute neutrophil count (ANC) less than 500 cells/mm³: Discontinue tocilizumab.

Platelet count 50,000 to 100,000 cells/mm³: Hold tocilizumab and restart when platelet count is greater than 100,000/mm³ with IV dosing at 4 mg/kg with an increase to 8 mg/kg as clinically appropriate or subcutaneous dosing at every other week with an increase to weekly as clinically appropriate.

Platelet count less than 50,000 cells/mm³: Discontinue tocilizumab.

Hepatic enzyme abnormalities: Dosage interruption or modifications are recommended based on the degree of abnormality occurring during treatment, as evidenced by the degree of AST/ALT elevations above the upper limit of normal (ULN).[38283]

Pediatric Patients

- Tocilizumab dose reduction has not been studied in the systemic juvenile idiopathic arthritis (SJIA) or polyarticular juvenile idiopathic arthritis (PJIA) population.
- Tocilizumab dose interruptions are recommended for low neutrophil counts and low platelet counts in patients with SJIA or PJIA at levels similar to what is outlined for adult patients with rheumatoid arthritis. If appropriate, concomitant methotrexate and/or other medications should be dose modified or stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. In SJIA and PJIA, base the decision to discontinue tocilizumab for a laboratory abnormality upon the medical assessment of the individual patient.[38283]

Maximum Dosage Limits

- Adults

Rheumatoid arthritis, weighing more than 100 kg: 800 mg/dose IV and 162 mg/dose subcutaneously.

Rheumatoid arthritis and giant cell arteritis, weighing 100 kg or less: 8 mg/kg/dose IV and 162 mg/dose subcutaneously.

Cytokine Release Syndrome (CRS), weighing 30 kg or more: 800 mg/dose IV.

CRS, weighing less than 30 kg: 12 mg/kg IV.

- Geriatric

Rheumatoid arthritis, weighing more than 100 kg: 800 mg/dose IV and 162 mg/dose subcutaneously.

Rheumatoid arthritis and giant cell arteritis, weighing 100 kg or less: 8 mg/kg/dose IV and 162 mg/dose subcutaneously.

Cytokine Release Syndrome (CRS), weighing 30 kg or more: 800 mg/dose IV.

CRS, weighing less than 30 kg: 12 mg/kg IV.

- Adolescents

Weighing 30 kg or more: 8 mg/kg/dose IV and 162 mg/dose subcutaneously.

Weighing less than 30 kg: 12 mg/kg/dose IV for systemic juvenile idiopathic arthritis (SJIA) and cytokine release syndrome (CRS); 10 mg/kg/dose IV for polyarticular juvenile idiopathic arthritis (PJIA); 162 mg/dose subcutaneously for SJIA and PJIA.

- Children

2 to 12 years weighing 30 kg or more: 8 mg/kg/dose IV and 162 mg/dose subcutaneously.

2 to 12 years weighing less than 30 kg: 12 mg/kg/dose IV for systemic juvenile idiopathic arthritis (SJIA) and cytokine release syndrome (CRS); 10 mg/kg/dose IV for polyarticular juvenile idiopathic arthritis (PJIA); 162 mg/dose subcutaneously for SJIA and PJIA.

Younger than 2 years: Safety and efficacy have not been established.

- Infants

Safety and efficacy have not been established.

Patients with Hepatic Impairment Dosing

Prior to treatment initiation

Do not initiate treatment with tocilizumab if active liver disease or hepatic impairment is present, or if baseline AST/ALT is more than 1.5 times the upper limit of normal (ULN). However, patients with severe or life-threatening cytokine release syndrome (CRS) frequently have elevated ALT or AST; the decision to administer tocilizumab should take into account the potential benefit of treating the CRS versus the risks of short-term treatment with tocilizumab.[\[38283\]](#)

Hepatic enzyme elevations that occur during treatment

Adult Patients with rheumatoid arthritis or giant cell arteritis with hepatic impairment[\[38283\]](#)

AST and/or ALT of more than 1 times and up to 3 times the ULN:

- Dose modify concomitant DMARDs, if appropriate.
- For persistent increases in this range:
 - Intravenous dosing: For persistent increases in this range, reduce IV tocilizumab dose to 4 mg/kg or hold tocilizumab dosing until AST and/or ALT have normalized.
 - Subcutaneous dosing: Reduce subcutaneous dosing interval to every other week or hold tocilizumab dosing until AST and/or ALT have normalized. Once ALT and/or AST have normalized, resume subcutaneous injection at every other week dosing and increase to once weekly as clinically appropriate.

AST and/or ALT more than 3 times and up to 5 times the ULN:

- Interrupt tocilizumab dosing until AST and/or ALT is less than 3 times the ULN and then follow dosing recommendations for AST and/or ALT more than 1 to 3 times ULN.
- For persistent increases of more than 3 times the ULN, discontinue tocilizumab.

AST and/or ALT greater than 5 times the ULN: Discontinue tocilizumab.

-Pediatric Patients with hepatic impairment[38283]

Tocilizumab dose reduction has not been studied in the systemic juvenile idiopathic arthritis (SJIA) or polyarticular juvenile idiopathic arthritis (PJIA) population. Tocilizumab dose interruptions are recommended for liver enzyme abnormalities in patients with SJIA or PJIA at levels similar to what is outlined for adult patients with rheumatoid arthritis and giant cell arteritis. If appropriate, adjust or stop concomitant DMARDs and hold tocilizumab dosing until the clinical situation has been evaluated. In SJIA and PJIA, base the decision to discontinue tocilizumab upon the medical assessment of the individual patient and the laboratory abnormality involved.

Patients with Renal Impairment Dosing

CrCl 30 mL/minute or more: No dosage adjustment is needed.

CrCl less than 30 mL/minute: Tocilizumab has not been studied in patients with severe renal impairment.[38283]

† Off-label indication

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References

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62883 – Khanna D, Denton CP, Jhreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomized, controlled trial. *Lancet* 2016;387:2630-40.

65148 – Italian Society of Infectious and Tropical Diseases. Handbook for the care of people with disease-COVI 19. Edition 2.0, March 13, 2020.

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How Supplied

Tocilizumab Solution for injection
Actemra 200mg/10mL Solution for Injection (50242-0136) (Genentech Inc)
Actemra 400mg/20mL Solution for Injection (50242-0137) (Genentech Inc)
Actemra 80mg/4mL Solution for Injection (50242-0135) (Genentech Inc)
Actemra 162mg/0.9mL Solution for Injection (50242-0138) (Genentech Inc)
Actemra ACTPen 162mg/0.9mL Solution for Injection (50242-0143) (Genentech Inc)

Description/Classification

Description

Tocilizumab is a humanized interleukin-6 (IL-6) receptor-inhibiting monoclonal antibody produced in mammalian (Chinese hamster ovary) cells. In patients with inflammatory diseases such as rheumatoid arthritis, IL-6 concentrations correlate with disease activity and joint or tissue damage. In adults, tocilizumab is FDA approved for the treatment of moderate to severe rheumatoid arthritis (RA) after inadequate response to disease-modifying antirheumatic drugs (DMARDs).[38283] In adults with rheumatoid arthritis (RA) tocilizumab improves clinical signs and symptoms, inhibits the radiographic progression of structural joint damage, and improves health status. In pediatric patients 2 years of age and older, tocilizumab is approved for polyarticular and systemic juvenile idiopathic arthritis (pJIA and sJIA).[38283] In adult and pediatric patients with inflammatory arthritis conditions, tocilizumab is often considered as an alternative to TNF-blockers or may be used when TNF-blockers have failed to produce adequate responses.[56233][61404] For RA, pJIA, and sJIA, tocilizumab may be used alone or in combination with methotrexate; in treating adult RA, other non-biologic DMARDs may also be used concurrently.[38283] The ideal combination of therapy for individual patients with inflammatory arthritis conditions is determined by treat to target strategies and severity of disease.[56233][61404] In adults, tocilizumab has proven effective for giant cell arteritis (GCA or temporal arteritis), where it is used initially with a tapering dose of corticosteroids.[38283] Additionally, the drug is approved in adult and pediatric patients 2 years and older for cytokine release syndrome (CRS) due to chimeric antigen receptor (CAR) T cell treatment.[38283] Tocilizumab labeling carries a boxed warning regarding the risk for serious infections that may lead to hospitalization or death; live vaccines should not be administered with tocilizumab. Severe hypersensitivity reactions, including anaphylaxis and death, have also been reported with tocilizumab therapy.[38283]

Updates for coronavirus disease 2019 (COVID-19):

Available data are limited. Due to a lack of clinical data, the National Institutes of Health (NIH) COVID-19 treatment guidelines do not give recommendations for or against the use of IL-6 receptor inhibitors, such as tocilizumab.[65314] Preliminary data suggest tocilizumab may have clinical benefit as adjunctive therapy in the treatment of COVID-19 due to SARS-CoV-2. In a retrospective review of 21 patients, tocilizumab was added to standard therapy. Clinical symptoms, CT opacity changes, lymphocyte percentage, and C-reactive protein levels all improved in these patients; however, no comparators were reported.[65162] Additional data regarding clinical efficacy for COVID-19 are being evaluated.[65148][65163][65191][65193][65194]

Classifications

- [Antineoplastic and Immunomodulating Agents](#)
 - [Agents that Suppress the Immune System](#)
 - [Interleukin-6 \(IL-6\) Inhibitors](#)

- [Musculo-Skeletal System](#)
 - [Antiinflammatory Agents and Antirheumatic Agents](#)
 - [Specific Anti-Rheumatic Agents](#)
 - [Anti-Rheumatic Monoclonal Antibodies](#)

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References

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61404 – Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res (Hoboken)*. 2011;63:465-482. Review.

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Administration Information

General Administration Information

For storage information, see the specific product information within the How Supplied section.

Route-Specific Administration

Injectable Administration

- Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit. Tocilizumab is a clear and colorless to pale yellow liquid.
- The prefilled syringe and the autoinjector are ONLY for subcutaneous injection use.
- The vial is ONLY for use in preparing an intravenous infusion.[38283]

Intravenous Administration

- Administer intravenous infusions under the supervision of a qualified health professional. Have appropriate medical treatment available for immediate use in the event of a serious hypersensitivity reaction.
- The drug must be diluted as an infusion prior to use. Do not administer as an intravenous push or bolus. [38283]

Infusion Preparation

- Compatible infusion solutions for preparation: 0.9% Sodium Chloride Injection or 0.45% Sodium Chloride Injection.
- Utilize a 50 mL infusion bag or bottle for patients who weigh less than 30 kg. Utilize a 100 mL infusion bag or bottle for patients who weigh at least 30 kg.
- From a 50 mL or 100 mL infusion bag or bottle, withdraw a volume of the 0.9% Sodium Chloride Injection or 0.45% Sodium Chloride Injection equal to the volume of the tocilizumab solution required for the patient's dose.
- Each tocilizumab vial contains a 20 mg/mL solution.
 - For a 4 mg/kg dose, 0.2 mL/kg of tocilizumab is needed.
 - For a 8 mg/kg dose, 0.4 mL/kg is needed.
 - For a 10 mg/kg dose, 0.5 mL/kg is needed.
 - For a 12 mg/kg dose, 0.6 mL/kg is needed.
- Withdraw the amount of tocilizumab for intravenous infusion from the vial(s) and slowly add to the infusion bag or bottle.
- Gently invert the bag to mix and to avoid foaming.
- Fully diluted tocilizumab solutions are compatible with polypropylene, polyethylene, and polyvinyl chloride infusion bags and polypropylene, polyethylene, and glass infusion bottles.
- *Storage:* The fully diluted tocilizumab solutions for infusion using 0.9% Sodium Chloride Injection may be stored at 2 to 8 degrees C (36 to 46 degrees F) or room temperature for up to 24 hours and should be protected from light. The fully diluted tocilizumab solutions for infusion using 0.45% Sodium Chloride Injection may be stored at 2 to 8 degrees C (36 to 46 degrees F) for up to 24 hours or at room temperature for up to 4 hours and should be protected from light. Do not freeze.
- Do not use any unused product remaining in vials; tocilizumab does not contain preservatives. [38283]

Intravenous Infusion Administration

- Prior to infusion, allow the fully diluted tocilizumab infusion to reach room temperature.
- Administer as an intravenous infusion over 60 minutes with an infusion set.
- Do not infuse tocilizumab concomitantly in the same intravenous line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of tocilizumab with other drugs. [38283]

Subcutaneous Administration

General information

- Administer the first injection of tocilizumab under the supervision of a qualified health professional. Have appropriate medical treatment available for immediate use in the event of a serious hypersensitivity reaction.
- Assess the suitability of the patient for home use after the first dose. Patients should inform their provider before administering the next dose if they experience any symptoms of an allergic reaction. Patients should seek immediate medical attention if they develop symptoms of serious allergic reactions.
- After the first dose, the subcutaneous injection may subsequently be given by the patient or patient's caregiver after proper training in injection technique, and a healthcare practitioner determines that it is appropriate.
- Pediatric patients may self-inject with the prefilled syringe if both the healthcare practitioner and the parent/legal guardian determines it is appropriate. The ability of pediatric patients to self-inject using the autoinjector has not been tested. [38283]

Prefilled Syringe:

- Remove the prefilled syringe from the refrigerator and allow it to sit at room temperature outside of the carton for 30 minutes. Do not warm tocilizumab in any other way.
- Pick an injection site such as the front of a thigh, the outer area of an upper arm, or the abdomen except for the 2-inch area around the navel. Do not inject into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.
- Rotate injection sites with each injection. Inject at least 1 inch from the last area injected.
- Remove the needle cap immediately before injection, and gently pinch a cleaned area of skin. Using a dart-like motion, insert the needle at a 45-degree or 90-degree angle. Release the pinched skin, and gently push the plunger all the way down to inject the full amount in the prefilled syringe (0.9 mL), which provides 162 mg of tocilizumab.
- The prefilled syringe is for single-use only, as it does not have a preservative.
- Remove the needle from the skin while continuing to depress the plunger. After the needle is completely removed, release the plunger, which will allow the needle-shield to protect the needle. Do not rub the injection site.
- Dispose of needles and syringes in an FDA-cleared sharps disposal container right away after use.[\[38283\]](#)

Autoinjector:

- Remove the autoinjector from the refrigerator and allow it to sit at room temperature outside of the carton for 45 minutes. Do not warm tocilizumab in any other way.
- Pick an injection site such as the front of a thigh, the outer area of an upper arm, or the abdomen except for the 2-inch area around the navel. Do not inject into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.
- Do not auto inject through clothing.
- Rotate injection sites with each injection. Inject at least 1 inch from the last area injected.
- Remove the needle cap immediately before injection, and gently pinch a cleaned area of skin. Place the needle-shield at a 90-degree angle against the pinched skin.
- Unlock the green activation button by firmly pressing the autoinjector against the pinched skin, then press the green button to start the injection. Continue to hold the autoinjector firmly against the skin until the purple indicator stops moving and the full dose administered; the complete injection may take up to 10 seconds.
- Release the green button and lift autoinjector off the skin at a 90-degree angle.
- The autoinjector is for single-use only, as it does not have a preservative. Dispose of needles and syringes in an FDA-cleared sharps disposal container right away after use.[\[38283\]](#)

Clinical Pharmaceutics Information

From Trissel's 2™ Clinical Pharmaceutics Database

Tocilizumab

1. pH Range

pH near 6.5 (vial). pH near 6.0 (prefilled syringe)

References

Actemra (tocilizumab) package insert. South San Francisco, CA. Genentech, Inc. 2019; Jun

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References

38283 – Actemra (tocilizumab) injection package insert. South San Francisco, CA: Genentech, Inc.; 2019 Jun.

Adverse Reactions

- abdominal pain
 - anaphylactic shock
 - anaphylactoid reactions
 - angioedema
 - antibody formation
 - arthralgia
 - candidiasis
 - cough
 - diarrhea
 - dizziness
 - dyspnea
 - elevated hepatic enzymes
 - fatigue
 - gastritis
 - GI perforation
 - headache
 - hepatic failure
 - hepatitis
 - hepatotoxicity
 - hypercholesterolemia
 - hyperlipidemia
 - hypertension
 - hypertriglyceridemia
 - hypotension
 - infection
 - infusion-related reactions
 - injection site reaction
 - jaundice
 - macrophage activation syndrome
 - neutropenia
 - new primary malignancy
 - optic neuritis
 - oral ulceration
 - pancreatitis
 - peripheral neuropathy
 - pharyngitis
 - pruritus
 - rash
 - Stevens-Johnson syndrome
 - thrombocytopenia
 - urticaria
 - visual impairment
 - weakness
-

Tocilizumab recipients are at increased risk for developing serious infections that may lead to hospitalization or death. Severe and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including tocilizumab. During and after treatment with tocilizumab, closely monitor all patients for the development of signs and symptoms of infection including the possible development of tuberculosis (TB) in patients who tested negative for latent TB infection before tocilizumab use. If a serious infection develops, interrupt tocilizumab until the infection is controlled. Carefully consider the risks and benefits of continued tocilizumab therapy in patients with chronic or recurrent infection.^[38283] Infections of various types were reported during clinical trials with tocilizumab. Upper respiratory tract infection occurred in 7% of rheumatoid arthritis patients receiving tocilizumab 8 mg/kg, in 6% of those receiving tocilizumab 4 mg/kg plus DMARDs, and in 8% of patients who received tocilizumab 8 mg/kg plus DMARDs. Naso-pharyngitis was reported in 4% to 7% of patients, and bronchitis was reported in 3% to 4% of patients. The rate of serious infections in the adult tocilizumab 4 mg/kg plus DMARD group was 4.4 events per 100 patient-years, and in the 8 mg/kg plus DMARD group, the rate was 5.3 events per 100 patient-years. Among pediatric patients who received tocilizumab, the rate of serious infections was 11.5 per 100 patient-years for those with systemic juvenile idiopathic arthritis (JIA), 12.2 per 100 patient-years for those with polyarticular JIA and weight less than 30 kg, and 4 per 100 patient-years for those with polyarticular JIA and a weight of 30 kg or more. There is an overall higher incidence of infections in patients with giant cell arteritis (GCA) compared to those with rheumatoid arthritis. The rate of infection or serious infection was 200.2/9.7 events per 100 patient-years in the weekly tocilizumab group and 160.2/4.4 events per 100 patient-years in the tocilizumab every other week group compared to 156/4.2 events per 100 patient-years in the placebo group receiving a 26-week prednisone taper and 210.2/12.5 events per 100 patient-years in the placebo group receiving a 52-week prednisone taper. The rate of serious infections in a cardiovascular outcomes study was 4.5 per 100 patient-years with tocilizumab 8 mg/kg IV, with or without DMARDs, every 4 weeks compared to 3.2 per 100 patient-years with etanercept 50 mg subcutaneously, with or without DMARDs. During clinical trials for any indication, the most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, otitis media, and bacterial arthritis. Among opportunistic infections, tuberculosis (pulmonary or extrapulmonary disease), cryptococcus infection, aspergillosis, candidiasis, and pneumocystosis were reported with tocilizumab. Patients who presented with disseminated rather than localized disease and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids. Viral reactivation has been reported with immunosuppressive biologic therapies and

cases of herpes zoster exacerbation were observed in tocilizumab clinical studies. No cases of hepatitis B reactivation were observed in the trials; however, patients who screened positive for hepatitis were excluded.[38283]

Gastrointestinal perforation primarily as a complication of diverticulitis was reported in clinical trials. The overall rate of GI perforation with IV tocilizumab was 0.26 events per 100 patient years. Most patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory drugs, corticosteroids, or methotrexate. The relative contribution of tocilizumab to the development of gastrointestinal perforations is unknown. Upper abdominal pain occurred in 2% of 288 patients who got tocilizumab 8 mg/kg, in 3% of 774 patients who got tocilizumab 4 mg/kg plus DMARDS, and in 3% of 1582 patients who got tocilizumab 8 mg/kg plus DMARDS. Gastritis occurred in 1% of 288 patients who got tocilizumab 8 mg/kg, in 1% of 774 patients who got tocilizumab 4 mg/kg plus DMARDS, and in 2% of 1582 patients who got tocilizumab 8 mg/kg plus DMARDS. Oral ulceration occurred in 2% of 288 patients who got tocilizumab 8 mg/kg, in 1% of 774 patients who got tocilizumab 4 mg/kg plus DMARDS, and in 2% of 1582 patients who got tocilizumab 8 mg/kg plus DMARDS. Use tocilizumab cautiously 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.[38283]

Tocilizumab may cause neutropenia, and patient's neutrophil counts need to be assessed before and during drug receipt. In the 6-month, controlled clinical studies for rheumatoid arthritis, decreases in neutrophil counts below 1,000/mm³ occurred in 1.8% of patients who received tocilizumab 4 mg/kg/dose and in 3.4% of patients who received tocilizumab 8 mg/kg/dose as compared with 0.1% of patients who received placebo. Decreases in neutrophil counts below 500/mm³ occurred in 0.4% of patients who received tocilizumab 4 mg/kg/dose and in 0.3% of patients who received tocilizumab 8 mg/kg/dose as compared with 0.1% of patients who received placebo. Approximately half of the instances of absolute neutrophil count (ANC) below 1,000/mm³ occurred within 8 weeks of starting tocilizumab. After subcutaneous tocilizumab receipt, 2.9% to 3.7% of tocilizumab recipients had a neutrophil count below 1,000/mm³. Among pediatric patients with polyarticular juvenile idiopathic arthritis (PJIA), 3.7% receiving IV treatment and 15.4% receiving subcutaneous treatment had a neutrophil count below 1,000/mm³ whereas 7% of patients with systemic juvenile idiopathic arthritis (SJIA) did (vs. none in the placebo group). Of note, neutropenia was more frequently observed in patients weighing less than 30 kg (25.9%) than those weighing 30 kg or more (4%) in the subcutaneous administration group. Over an average duration of 73 weeks, a decreased neutrophil count occurred in 17% of tocilizumab recipients. Infections have been uncommonly reported in association with treatment-related neutropenia in long-term extension studies and postmarketing clinical experience, and no clear relationship between decreases in neutrophils below 1,000/mm³ and the occurrence of serious infections was noted. Among healthy patients who received tocilizumab 2 to 28 mg/kg/dose, the ANC nadir occurred 3 to 5 days after tocilizumab receipt. Neutrophils then recovered towards baseline in a dose dependent manner. A similar pattern of ANC after tocilizumab receipt was noted in patients with rheumatoid arthritis.[38283]

Tocilizumab may cause thrombocytopenia, and patient's platelet counts need to be assessed before and during drug receipt. In the 6-month, controlled clinical studies for rheumatoid arthritis, decreases in platelet counts below 100,000/mcL occurred in 1.3% of patients who received tocilizumab 4 mg/kg and in 1.7% of patients who received tocilizumab 8 mg/kg as compared with 0.5% of patients who received placebo. Among patients with polyarticular juvenile idiopathic arthritis (PJIA), 1% had decreases in platelet count of 50,000/mcL or less. Of patients with systemic juvenile idiopathic arthritis (SJIA), decreases in platelet count of no more than 100,000/mcL were noted in 1% of tocilizumab recipients and in 3% of placebo recipients at the end of the 12-week control phase. Over an average duration of 73 weeks, 4% of tocilizumab recipients had a decreased platelet count. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials.[38283]

Serious cases of hepatotoxicity have been reported with intravenous and subcutaneous tocilizumab therapy; some of these cases resulted in hepatic failure, liver transplant, or death. A majority of the cases presented with elevated hepatic enzymes more than 5 times the upper limit of normal (ULN); however, other cases presented with mild elevations along with signs and symptoms of liver impairment. The time to onset ranged from weeks to years following initiation of tocilizumab therapy, with a median latency of 98 days. Hepatitis, drug-induced liver injury, and jaundice have been reported with postmarketing use of tocilizumab. Patients should have liver function tests (LFTs) monitored during tocilizumab treatment. Check LFTs before tocilizumab receipt, 4 to 8 weeks after the start of therapy for the first 6 months, and then every 3 months thereafter in adult patients. For pediatric patients with either polyarticular or systemic juvenile idiopathic arthritis (PJIA or SJIA), monitor LFTs at the time of the second infusion and then every 4 to 8 weeks for PJIA and every 2 to 4 weeks for SJIA.[38283] [65165] In the 6-month, controlled clinical studies for rheumatoid arthritis, 36% of patients who received tocilizumab 8 mg/kg monotherapy developed an ALT up to 3 times the ULN and 22% experienced AST levels up to 3 times the ULN. Increases in ALT greater than 3 to 5 times ULN occurred in 1%, and increases in ALT of more than 5 times ULN occurred in 0.7%. In a study of 1,538 patients with moderate to severe rheumatoid arthritis, 5.3% and 2.2% of patients developed ALT or AST elevations more than 3 times the ULN, respectively. In addition, one patient developed serious drug-induced hepatitis with hyperbilirubinemia. Increased frequency and magnitude of transaminase elevations were observed when

potentially hepatotoxic drugs were used in combination with tocilizumab. For example, among 1,582 patients who received 8 mg/kg tocilizumab plus DMARDs, increases in ALT up to 3 times ULN, greater than 3 to 5 times the ULN, and greater than 5 times the ULN occurred in 48%, 5%, and 1.5% of patients, respectively. Modification of the treatment regimen, such as a reduction in the concomitant DMARD dose, tocilizumab interruption, or tocilizumab dose reduction resulted in a decrease or normalization of liver enzymes. Among pediatric patients with PJIA, 4% had ALT levels 3 times ULN or greater, and less than 1% had AST levels 3 times ULN or greater. Among patients with SJIA, 5% had ALT levels 3 times ULN or greater, and 3% had AST levels greater than 3 times ULN. Over an average duration of 73 weeks in the SJIA extension study, ALT levels 3 times ULN or higher were noted in 13%, and AST levels 3 times ULN or greater were noted in 5%. Among adult patients with rheumatoid arthritis, increases in ALT levels 3 times ULN or greater were noted in 6.5% of weekly subcutaneous tocilizumab recipients and in 3.4% of every other week recipients. [38283]

Tocilizumab may cause hyperlipidemia and hypertriglyceridemia, and patient's lipid parameters need to be assessed during drug receipt. In clinical trials, lipid parameters were first assessed 6 weeks after tocilizumab initiation. Increases in total cholesterol, LDL, HDL, and triglycerides were noted at this time point, but the concentrations remained stable with continued tocilizumab receipt. Triglyceride concentrations greater than 500 mg/dL were rarely observed. In regard to hypercholesterolemia, the mean LDL increase from baseline to week 24 was 25 mg/dL among recipients of tocilizumab 8 mg/kg IV as monotherapy. The mean HDL increase was 4 mg/dL, and the mean LDL/HDL ratio increased by 0.26. ApoB/ApoA1 ratios were essentially unchanged, and elevated lipids responded to lipid-lowering agents. After SC tocilizumab for rheumatoid arthritis, sustained elevations in total cholesterol more than 240 mg/dL were noted in 19% of weekly tocilizumab recipients, in 19.6% of every other week tocilizumab recipients, and in 10.2% of placebo recipients. Among patients with systemic juvenile idiopathic arthritis, 1.5% of tocilizumab recipients had a total cholesterol concentration more than 1.5 to 2 times the upper limit of normal (ULN) as compared with none of the placebo recipients. Assess lipid parameters approximately 4 to 8 weeks after tocilizumab initiation. Subsequently, it is recommended to manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.[38283]

Tocilizumab may increase the risk of a new primary malignancy. Tocilizumab is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of cancer. Malignancies were observed in clinical studies for rheumatoid arthritis, but the impact of tocilizumab receipt on the development of malignancies is not known. Over 6 months, 15 malignancies were diagnosed in tocilizumab IV recipients as compared with 8 malignancies in patients in the control groups. Exposure-adjusted incidence was similar in the tocilizumab groups (1.32 events per 100 patient-years) and in the placebo plus DMARD group (1.37 events per 100 patient-years). In the all-exposure population, the rate of malignancies remained consistent with the rate observed in the 24-week, controlled period.[38283]

Postmarketing reports of anaphylaxis, anaphylactic shock, anaphylactoid reactions (such as angioedema), and death have occurred in patients receiving a range of IV tocilizumab doses, with or without concomitant arthritis therapies, and in patients who have received premedication. Stevens-Johnson syndrome also has been reported with the postmarketing use of IV tocilizumab. In clinical trials, anaphylaxis or hypersensitivity reactions requiring therapy discontinuation were generally observed during the second to fourth tocilizumab IV infusion and were reported in 0.1% of 2,644 patients in the 6-month, controlled trials and in 0.2% of 4,009 patients in the all-exposure population for rheumatoid arthritis. As a comparison, hypersensitivity reactions that required treatment discontinuation were reported in 0.7% of 1,068 patients in the subcutaneous 6-month controlled trials and in 0.7% of 1,465 patients in the subcutaneous all-exposure population for rheumatoid arthritis. For pediatric patients who received IV tocilizumab, none of the 188 patients with polyarticular juvenile idiopathic arthritis and 0.9% of 112 patients with systemic juvenile idiopathic arthritis had hypersensitivity reactions that required treatment discontinuation. Six of 54 pediatric patients with systemic juvenile idiopathic arthritis (SJIA) developed a hypersensitivity reaction during or within 24 hours of an intravenous tocilizumab infusion; 3 were considered serious and removed from the study. Examples of reactions that required treatment discontinuation included generalized erythema, rash, and urticaria. Infusion-related reactions defined as events that occurred during or within 24 hours of tocilizumab receipt were noted in 4% to 20.2% of patients and consisted of hypertension, headache, nausea, hypotension, dizziness, rash, pruritus, urticaria, diarrhea, epigastric discomfort, and arthralgia. In clinical trials of IV tocilizumab for rheumatoid arthritis, rash occurred in 2% to 4% of patients, dyspnea or cough in less than 2%, hypertension in 4% to 6%, headache in 5% to 7%, and dizziness in 2% to 3%. Consider the diagnosis of hypersensitivity or anaphylaxis in any patient who has an infusion reaction. Only administer tocilizumab IV if appropriate medical support to manage anaphylaxis is available. Immediately stop the infusion and institute appropriate medical management if an anaphylactic or other serious hypersensitivity reaction occurs. For subcutaneous administration, instruct patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. Permanently discontinue tocilizumab if a hypersensitivity reaction occurs; tocilizumab is contraindicated for use by patients with known hypersensitivity to the drug. Despite prompt medical intervention, a woman died within 24 hours of an anaphylactic event. She experienced lightheadedness and hypotension during her fourth tocilizumab infusion, which was stopped after her symptoms developed. During her fifth infusion 2 weeks later, she experienced dizziness and hypotension moments after the start

of the infusion despite premedication with steroids and antihistamines. She became apneic and unresponsive before dying. If a hypersensitivity or infusion-related reaction occurs, please report the event to the manufacturer by calling 1-888-835-2555.[38283] [43101]

A mild to moderate injection site reaction (7.1% to 10%) including erythema, pruritus, pain, and hematoma has been noted with subcutaneous tocilizumab administration in adult patients. As a comparison, 2.4% to 4.1% of subcutaneous placebo recipients had a local reaction. A higher frequency of injection site reaction (28.8% to 41.2%) was observed in pediatric patients receiving subcutaneous tocilizumab. All reactions were mild in severity, but, in the polyarticular arthritis group, occurred more commonly in patients weighing 30 kg or more (44%) compared to those weighing less than 30 kg (14.8%). The majority of injection site reactions resolved without any treatment, and none necessitated drug discontinuation.[38283]

Tocilizumab may increase the risk of macrophage activation syndrome (hemophagocytic lymphohistiocytosis or MAS), which is a life-threatening disorder that may develop in patients with rheumatic conditions, especially systemic juvenile idiopathic arthritis (SJIA). Limited data from clinical development experience do not suggest that tocilizumab increases the incidence of MAS; during clinical trials for SJIA, 3 cases were observed in 112 patients who received tocilizumab. Two patients had tocilizumab receipt interrupted, and one patient had tocilizumab discontinued for MAS. All three received treatment, and the MAS resolved without sequelae. Of note, infection is a trigger for MAS, and tocilizumab is associated with an increased risk of serious infections. Be attentive to symptoms of infection or worsening arthritis symptoms; SJIA worsening is also a trigger for macrophage activation syndrome.[38283] [54707]

Antibody formation against tocilizumab occurred in 46 of 2,876 adult patients with rheumatoid arthritis (1.6%) who received IV tocilizumab; 5 of the 46 had an associated, medically significant hypersensitivity reaction that led to tocilizumab withdrawal. Thirty adult patients developed neutralizing antibodies to tocilizumab. In polyarticular juvenile idiopathic arthritis trials, 1 patient receiving IV tocilizumab and 3 patients receiving subcutaneous tocilizumab developed positive antibodies without developing a clinically significant hypersensitivity reaction. Of the 2 patients in the systemic juvenile idiopathic arthritis (SJIA) trials that developed positive antibodies, one patient experienced symptoms associated with an anaphylactic reaction (urticaria and angioedema) and the other developed macrophage activation syndrome; both patients discontinued therapy. After subcutaneous drug receipt, 0.9% of 1,454 adult patients with rheumatoid arthritis developed anti-tocilizumab antibodies, and all but 1 patient also developed neutralizing antibodies. The rate is consistent with previous IV experience, and no correlation of antibody development to adverse events or loss of clinical response was observed.[38283]

Pancreatitis has been reported with the postmarketing use of tocilizumab.[38283]

Multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies of tocilizumab. Closely monitor patients for signs and symptoms potentially indicative of demyelinating disorders, such as optic neuritis or other visual impairment, peripheral neuropathy (numbness or tingling), or unusual fatigue or weakness.[38283]

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References

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43101 – Genentech Dear Healthcare Professional letter, September 2010. Important safety information regarding tocilizumab (Actemra/Roactemra).

54707 – Kumar MK, Suresh MK, Dalus D. Macrophage activation syndrome. J Assoc Physicians India 2006;54:238-40.

65165 – Genentech Dear Healthcare Professional letter, June 2019. Important drug warning regarding tocilizumab (Actemra).

Contraindications/Precautions

Absolute contraindications are italicized.

- breast-feeding
- children

- corticosteroid therapy
- diabetes mellitus
- diverticulitis
- fungal infection
- geriatric
- GI perforation
- hepatic disease
- hepatitis
- hepatitis B exacerbation
- hepatotoxicity
- human immunodeficiency virus (HIV) infection
- hypercholesterolemia
- hyperlipidemia
- hypertriglyceridemia
- immunosuppression
- infants
- infection **B**
- influenza
- jaundice
- labor
- multiple sclerosis
- neonates
- neoplastic disease
- neurological disease
- neutropenia
- new primary malignancy
- obstetric delivery
- pregnancy
- sepsis
- surgery
- thrombocytopenia
- tuberculosis
- vaccination

Tocilizumab is contraindicated for use by patients with *known hypersensitivity to tocilizumab*. Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with infusion of tocilizumab. Appropriate medical treatment should be available for immediate use in the event of an anaphylactic reaction during drug administration.[\[38283\]](#)

Patients who receive tocilizumab are at increased risk for developing serious infections that may lead to hospitalization or death. Infections include active tuberculosis and invasive fungal infections including candidiasis, aspergillosis, and pneumocystis. Bacterial, viral, and other infections due to opportunistic pathogens have been reported. Most patients who developed serious infections were taking concomitant immunosuppressives such as methotrexate or corticosteroids. Patients who have surgery while taking tocilizumab may be at greater risk for postoperative infections. Patients with an invasive fungal infection may present with disseminated disease, and tuberculosis may present as pulmonary or extrapulmonary disease. Evaluate patients for tuberculosis risk factors before starting tocilizumab. Also, test patients for latent tuberculosis before and during tocilizumab receipt. Initiate treatment for latent infection before tocilizumab use. Consider anti-tuberculosis therapy prior to tocilizumab initiation for 2 patient groups: patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed and patients with a negative test for latent tuberculosis but with risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Carefully consider the risks and benefits of tocilizumab before initiating therapy in patients with chronic or recurrent infection, who have been exposed to tuberculosis, with a history of a serious or opportunistic infection, with underlying conditions that may predispose them to infection (e.g., patients with advanced or uncontrolled diabetes mellitus, human immunodeficiency virus (HIV) infection, or immunosuppression), or who have resided or traveled in areas of endemic tuberculosis or endemic mycoses. Tocilizumab initiation is not recommended for patients with an absolute neutrophil count (ANC) less than 2,000/mm³, tocilizumab discontinuation is advised for an ANC less than 500/mm³, and tocilizumab interruption is advised for an ANC between 500/mm³ and 1000/mm³. Closely monitor patients for the development of signs and symptoms of infection during and after tocilizumab treatment; signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants. Consider the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to taking tocilizumab. Do not administer tocilizumab to a patient with an active infection including localized infections. If a serious infection such as sepsis or influenza or an opportunistic infection develops, interrupt tocilizumab receipt until the infection is controlled. If a new infection develops during tocilizumab receipt, complete a prompt and complete diagnostic workup appropriate for an immunocompromised patient, initiate appropriate antimicrobial therapy, and closely monitor the patient.

Initiation of tocilizumab is not recommended for thrombocytopenia defined as a platelet count below 100,000 cells/mm³ or for neutropenia defined as an absolute neutrophil count (ANC) below 2,000 cells/mm³. Thrombocytopenia and neutropenia have been noted with tocilizumab, and drug interruption or discontinuation may be needed. Check platelet count and ANC before tocilizumab receipt, 4 to 8 weeks after tocilizumab initiation, and every 3 months thereafter for adult patients. For pediatric patients with either polyarticular or systemic juvenile idiopathic arthritis (JIA), monitor neutrophils and platelets at the time of the second infusion and then every 4 to 8 weeks for PJIA and every 2 to 4 weeks for SJIA. In patients with severe or life-threatening cytokine release syndrome

(CRS) who also have cytopenias due to lymphodepleting chemotherapy or the CRS, consider the potential benefit of treating the CRS versus the risks of short-term treatment with tocilizumab.[\[38283\]](#)

Use tocilizumab with caution in patients with active hepatic disease or hepatic impairment. Initiation of tocilizumab is not recommended in patients who have ALT or AST above 1.5 times the upper limit of normal (ULN). Hepatotoxicity, including hepatic injury, hepatic failure, liver transplant, and death have been reported with tocilizumab therapy. Following tocilizumab initiation, the time to onset of hepatic injury ranged from months to years, and a majority of the patients presented with transaminases levels greater than 5 times the upper limit of normal (ULN). However, some patients had mild transaminase elevations along with signs and symptoms of liver impairment. Persistent hepatic enzyme elevations during therapy may require dose interruption or consideration of drug discontinuation, depending on the clinical abnormality and severity. Check liver function tests before tocilizumab receipt, 4 to 8 weeks after the start of therapy for the first 6 months, and then every 3 months after that in adult patients. For pediatric patients with either polyarticular or systemic juvenile idiopathic arthritis (JIA), monitor liver function tests at the time of the second infusion and then every 4 to 8 weeks for PJIA and every 2 to 4 weeks for SJIA. Liver function tests (LFTs) should also be measured in any patient displaying signs and symptoms of liver dysfunction, such as fatigue, anorexia, dark urine, jaundice, or right upper abdominal pain. If elevated LFTs are detected, then tocilizumab should be stopped and only restarted once liver enzymes have normalized and an alternative cause identified. In patients with severe or life-threatening cytokine release syndrome (CRS) who also have elevated hepatic enzymes due to lymphodepleting chemotherapy or the CRS, consider the potential benefit of treating the CRS versus the risks of short-term treatment with tocilizumab. The safety and efficacy of tocilizumab have not been studied in patients with positive hepatitis B virus (HBV) or hepatitis C virus (HCV) serology. Tocilizumab may cause HBV or HCV reactivation in patients who are HBV or HCV carriers, which may lead to hepatitis C or hepatitis B exacerbation. Consider evaluating patients at risk for HBV and HCV infection for prior evidence of infection before tocilizumab initiation. If tocilizumab is initiated in an HBV or HCV carrier, carefully monitor the patient for clinical and laboratory signs of active HBV or HCV infection.[\[38283\]](#)

Cautious use of tocilizumab may be warranted by patients with neurological disease such as preexisting or recent onset demyelinating disorders. The impact of tocilizumab on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies. Closely monitor patients for signs and symptoms potentially indicative of demyelinating disorders.[\[38283\]](#)

Gastrointestinal (GI) perforations and other GI adverse reactions have been reported in clinical studies of tocilizumab. GI perforation risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroid therapy. Promptly evaluate patients presenting with new onset abdominal symptoms. Cautious tocilizumab use is warranted by patients with diverticulitis.[\[38283\]](#)

Tocilizumab is an immunosuppressant and treatment with immunosuppressants may result in an increased risk of cancer. The impact of tocilizumab on the development of a new primary malignancy is unknown, but malignancies were observed in clinical studies. Consider the risks and benefits of tocilizumab before treatment initiation in patients with a history of neoplastic disease. Also, consider the risks and benefits of tocilizumab continuation in patients who develop a malignancy.[\[38283\]](#)

Cautious use of tocilizumab may be warranted for patients with hyperlipidemia, hypercholesterolemia, or hypertriglyceridemia. Increased total cholesterol, increased HDL-C, increased LDL-C, and increased triglycerides may occur with tocilizumab. Assess lipid parameters approximately 4 to 8 weeks after tocilizumab initiation. Subsequently, it is recommended to manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.[\[38283\]](#)

Avoid use of live vaccines concurrently with tocilizumab as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab. No data are available on the effectiveness of vaccination in patients receiving tocilizumab. Because IL-6 inhibition may interfere with the normal immune response to new antigens, it is recommended that all treated patients, particularly pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating tocilizumab therapy. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.[\[38283\]](#)

In clinical trials for rheumatoid arthritis, the frequency of serious infections among geriatric patients was higher as compared with the frequency among younger adult patients. As there is a higher incidence of infections in the geriatric population in general, caution should be used when treating the elderly. Clinical studies that for cytokine release syndrome did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.[\[38283\]](#)

Limited available data are not sufficient to determine whether the use of tocilizumab during human pregnancy is associated with risk for major birth defects or miscarriage. Based on animal data, there may be a potential risk to the fetus. In animal reproduction studies, intravenous administration of tocilizumab to Cynomolgus monkeys during organogenesis resulted in abortion/embryo-fetal death at doses 1.25 times or more of the maximum recommended human dose (MRHD). Monoclonal antibodies, like tocilizumab, are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. This may affect the immune response in the in utero exposed infant; consider risks and benefits before administering live or live-attenuated vaccines to neonates or infants exposed to tocilizumab in utero. A pregnancy registry has been established to monitor maternal and fetal outcomes; health care providers are encouraged to register pregnant women exposed to tocilizumab by calling 1-877-311-8972.[38283] Due to limited data during pregnancy, guidelines state that tocilizumab should be replaced before conception by another medication, if possible. The drug should be used during pregnancy only when no other pregnancy-compatible drug can effectively control the maternal disease.[62180] Tocilizumab may affect labor and obstetric delivery. Inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity, leading to potential delays in parturition.[38283]

The lack of clinical data during lactation precludes clear determination of the risk of tocilizumab to the breast-feeding infant; therefore the developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for tocilizumab and the potential adverse effects on the breastfed child from exposure to the drug or the underlying maternal condition. There is no information available on the presence of tocilizumab in human milk or its effects on the breast-fed infant or milk production. Maternal immunoglobulin G (IgG) is present in human milk. If tocilizumab is transferred into human milk, the effects of local exposure in the gastrointestinal (GI) tract and potential limited systemic exposure in the infant to tocilizumab are unknown.[38283] Until more data are available, guidelines state that tocilizumab should generally be avoided during breast-feeding if another therapy is available to control the maternal disease. The drug has a large molecular weight, and experts suggest the oral bioavailability of any drug exposure to the infant through the GI tract is likely low. Breast-feeding should not be discouraged, however, when using the drug if no other options are available.[62180]

Tocilizumab is indicated in pediatric patients 2 years of age and older for the treatment of active systemic or polyarticular juvenile idiopathic arthritis (JIA) or cytokine release syndrome (CRS). The safety and efficacy of tocilizumab in infants and young children less than 2 years of age have not been established. It is recommended that all pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating tocilizumab therapy. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.[38283]

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62180 – Gotestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis.* 2016;75:795-810.

Mechanism of Action

Tocilizumab inhibits IL-6-mediated signaling by competitively binding to both soluble and membrane-bound IL-6 receptors. IL-6 is a proinflammatory cytokine that is involved in diverse physiological processes such as T-cell activation, immunoglobulin secretion induction, hepatic acute-phase protein synthesis initiation, and hematopoietic precursor cell proliferation and differentiation stimulation. IL-6 is produced by various cell types, including T- and B-cells, lymphocytes, monocytes, and fibroblasts. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis.[38283]

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Pharmacokinetics

Tocilizumab is administered subcutaneously or intravenously as an infusion. The pharmacokinetics of tocilizumab is characterized by nonlinear elimination which is a combination of linear clearance and Michaelis-Menten elimination. The nonlinear part of tocilizumab elimination leads to an increase in exposure that is more than dose-proportional. The pharmacokinetic parameters of tocilizumab do not change with time. Due to the dependence of total clearance on tocilizumab serum concentrations, the half-life of tocilizumab is also concentration-dependent and varies depending on the serum concentration level. At higher concentrations, clearance is mainly determined by the linear clearance, which was estimated to be 12.5 mL/hour. Linear clearance increases with body size. The concentration-dependent nonlinear clearance plays a major role at low concentrations. The half-life of tocilizumab is dependent on the concentration.[\[38283\]](#)

A population pharmacokinetic model, based on data in rheumatoid arthritis patients who received either intravenous or subcutaneous tocilizumab, found a terminal half-life of approximately 21.5 days at high serum concentrations and linear clearance of tocilizumab. Among adult patients with rheumatoid arthritis (RA), the tocilizumab volume of distribution (Vd) at steady-state was 6.4 L: the central Vd was 3.5 L, and the peripheral Vd was 2.9 L. For patients with rheumatoid arthritis, the concentration-dependent apparent half-life at steady-state is up to 11 days for 4 mg/kg/dose IV, up to 13 days for 8 mg/kg/dose IV every 4 weeks, up to 13 days for 162 mg subcutaneously every week, and 5 days for 162 mg subcutaneously every other week. For adults with giant cell arteritis (GCA) at steady-state, the effective half-life for 162 mg subcutaneously every week and every other week was 18.3 to 18.9 days and 4.2 to 7.9 days, respectively.[\[38283\]](#)

Decreases in C-reactive protein to within normal ranges were seen as early as week 2 after tocilizumab 4 mg/kg/dose or 8 mg/kg/dose initiation in adults with RA. Decreases in rheumatoid factor, erythrocyte sedimentation rate, serum amyloid A, fibrinogen, and increases in hemoglobin were noted with both tocilizumab doses, but the greatest improvements were noted with the 8 mg/kg dose. Population pharmacokinetic analyses in any patient population tested so far indicate no relationship between apparent clearance and the presence of anti-drug antibodies.[\[38283\]](#)

Affected cytochrome P450 (CYP450) isoenzymes and drug transporters: Unknown, possibly influences CYP enzyme activity

In vitro data suggest that IL-6 reduces mRNA expression for several CYP450 isoenzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and this reduced expression was reversed by cocubation with tocilizumab at clinically relevant concentrations. Accordingly, inhibition of IL-6 signaling in patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of the drug, leading to increased metabolism of drugs that are CYP450 substrates. The drug's effect on CYP2C8 or drug transporters (e.g., P-glycoprotein) is unknown.[\[38283\]](#)

The restoration of CYP450 enzyme activities may be clinically relevant for CYP450 substrate drugs with a narrow therapeutic index (NTI), where the dose is individually adjusted. Upon initiation of tocilizumab, therapeutic monitoring of the effect or drug concentration of the NTI drug should be performed; adjust the dose of the NTI drug as needed. Caution should be exercised when tocilizumab is coadministered with drugs where a decrease in effectiveness is undesirable (e.g., oral contraceptives, which are CYP3A4 substrates). The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab.[\[38283\]](#)

Route-Specific Pharmacokinetics

- **Intravenous Route**

After receipt of either 4 mg/kg/dose IV or 8 mg/kg/dose IV every 4 weeks, a more than dose-proportional increase in systemic exposure and in the trough concentration was noted. At steady-state, the mean

concentration with 8 mg/kg dosing was 3-fold higher than the systemic exposure after 4 mg/kg dosing. The trough concentration at steady-state with 8 mg/kg dosing was 134-fold higher than the trough concentration after 4 mg/kg dosing. In contrast, the maximum tocilizumab concentration increased dose-proportionally. After 4 mg/kg/dose IV every 4 weeks, the estimated median (range) C_{mean} at steady-state was 18 mcg/mL (8.9 to 50.7 mcg/mL), the median (range) steady-state C_{min} was 0.1 mcg/mL (0.0 to 14.6 mcg/mL), and the median (range) steady-state C_{max} was 86.1 mcg/mL (44.8 to 202 mcg/mL). Ninety percent of steady-state was reached after the first dose for C_{max} and AUC and after the fourth dose for C_{min}. After 8 mg/kg/dose IV every 4 weeks, the median (range) C_{mean} at steady-state was 54 mcg/mL (17 to 260 mcg/mL), the median (range) C_{min} at steady-state 13.4 mcg/mL (0.1 to 154 mcg/mL), and median (range) C_{max} at steady-state was 176 mcg/mL (75.4 to 557 mcg/mL). Approximately 90% of steady-state was reached after the first dose for C_{max}, after the third dose for AUC, and after the fourth dose for C_{min}.[\[38283\]](#)

- **Subcutaneous Route**

After weekly or every other week of 162 mg subcutaneous tocilizumab receipt to patients with rheumatoid arthritis (RA), steady-state was achieved after 10 weeks and 12 weeks, respectively. At steady state, the estimated median (range) C_{mean} was 47.3 mcg/mL (2.4 to 147 mcg/mL), C_{min} was 42.9 mcg/mL (1.3 to 144 mcg/mL), and C_{max} was 49.8 mcg/mL (3 to 150 mcg/mL) with once-weekly subcutaneous dosing. After every other week subcutaneous dosing, the estimated median (range) C_{mean} was 9.2 mcg/mL (0.2 to 43.6 mcg/mL), C_{min} was 4.1 mcg/mL (0.0 to 34.2 mcg/mL), and C_{max} was 12.1 mcg/mL (0.4 to 49.3 mcg/mL) at steady-state. Systemic exposures with once-weekly dosing were 5.1-fold higher for C_{mean} and 10.5-fold higher for C_{min} compared to every other week dosing. Accumulation for C_{min} was greater following subcutaneous, both once weekly and every other week regimens, compared to intravenous administration and is expected based on the non-linear clearance at lower concentrations. Greater than 90% of the steady-state value for C_{max} was achieved after the fifth dose with the once-weekly regimen and 12th dose with every other week regimen. Ninety percent of the steady-state values for the C_{mean} and C_{min} were achieved after the 6th and 12th injections, for the every other week and once-weekly regimens, respectively.[\[38283\]](#)

In patients, at steady-state, with giant cell arteritis (GCA) who received 162 mg tocilizumab subcutaneously every week, the estimated median (range) C_{max} was 72.1 mcg/mL (12.2 to 151 mcg/mL), C_{min} was 67.2 mcg/mL (10.7 to 145 mcg/mL), and C_{mean} was 70.6 mcg/mL (11.7 to 149 mcg/mL). For patients at steady-state who received 162 mg every other week, the estimated median (range) C_{max}, C_{min}, and C_{mean} were 17.2 mcg/mL (1.1 to 56.2 mcg/mL), 7.7 mcg/mL (0.1 to 37.3 mcg/mL), and 13.7 mcg/mL (0.5 to 49 mcg/mL), respectively. Steady-state was reached at 17 weeks and 14 weeks following once weekly and every other week dosing regimens, respectively.[\[38283\]](#)

Special Populations

- **Hepatic Impairment**

No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab was conducted; treatment with tocilizumab is not recommended in patients with active hepatic disease or hepatic impairment.[\[38283\]](#)

- **Renal Impairment**

Mild to moderate renal impairment defined as a CrCl 30 to 79 mL/minute did not impact the pharmacokinetic parameters of tocilizumab during clinical trials for various indications; no dosage adjustments are needed for patients with mild to moderate renal impairment.[\[38283\]](#)

- **Pediatrics**

Children and Adolescents 2 to 17 years

Polyarticular juvenile idiopathic arthritis (PJIA)

In pediatric patients with PJIA, the central volume of distribution (Vd) of tocilizumab is 1.98 L, and the peripheral Vd is 2.1 L, resulting in a steady-state Vd of 4.08 L. Linear clearance is 5.8 mL/hour. Half-life is up to 17 days for IV administration or 10 days for subcutaneous administration.[38283]

Average and trough concentrations of tocilizumab at steady-state in pediatric patients (dose = 8 mg/kg/dose or 10 mg/kg/dose IV every 4 weeks) are comparable to those observed in adult rheumatoid arthritis (RA) patients receiving 4 mg/kg/dose or 8 mg/kg/dose IV every 4 weeks and peak concentration similar to adult dose of 8 mg/kg/dose IV every 4 weeks in adult RA patients. The average concentration (C_{mean}) of tocilizumab in PJIA patients is slightly lower compared than that observed in adult RA patients. For doses of 8 mg/kg/dose IV every 4 weeks (patients weighing 30 kg or more), estimated median C_{max}, C_{min}, and C_{mean} were 181 mcg/mL, 3.28 mcg/mL, and 38.6 mcg/mL, respectively, during pharmacokinetic trials. For doses of 10 mg/kg/dose IV every 4 weeks (patients weighing less than 30 kg), estimated median C_{max}, C_{min}, and C_{mean} were 167 mcg/mL, 0.35 mcg/mL, and 30.8 mcg/mL, respectively.[38283]

Bioavailability for subcutaneous tocilizumab in PJIA patients is 96%, and the absorption half-life is around 2 days. Average trough concentrations in pediatric patients after subcutaneous dosing are within the range of those achieved in adult patients with RA. Patients treated with subcutaneous tocilizumab have a steady-state C_{min} at or higher than that achieved with IV administration. In general, steady-state C_{min} is comparable in patients in both body weight groups (less than 30 kg and 30 kg or more), while steady-state C_{max} and C_{mean} are higher for patients in the lower weight group. For doses of 162 mg subcutaneous every 2 weeks (patients weighing 30 kg or more), estimated median C_{max}, C_{min}, and C_{mean} were 29.7 mcg/mL, 12.7 mcg/mL, and 23 mcg/mL, respectively, during pharmacokinetic trials. For doses of 162 mg subcutaneous every 3 weeks (patients weighing less than 30 kg), estimated median C_{max}, C_{min}, and C_{mean} were 62.4 mcg/mL, 13.4 mcg/mL, and 35.7 mcg/mL, respectively.[38283]

Systemic juvenile idiopathic arthritis (SJIA)

In pediatric patients with SJIA, the central Vd of tocilizumab is 1.87 L, and the peripheral Vd is 2.14 L, resulting in a steady-state Vd of 4.01 L. Linear clearance is 5.7 mL/hour. Half-life is up to 16 days for IV administration or 14 days for subcutaneous administration.[38283]

For doses of 8 mg/kg/dose IV every 2 weeks (patients weighing 30 kg or more), estimated median C_{max}, C_{min}, and C_{mean} were 253 mcg/mL, 70.7 mcg/mL, and 117 mcg/mL, respectively, during pharmacokinetic trials. For doses of 12 mg/kg/dose IV every 2 weeks (patients weighing less than 30 kg), estimated median C_{max}, C_{min}, and C_{mean} were 274 mcg/mL, 65.9 mcg/mL, and 124 mcg/mL, respectively. Steady-state was reached by 8 weeks for both groups. Mean estimated tocilizumab exposure parameters were similar between the 2 dose groups defined by body weight.[38283]

Bioavailability for subcutaneous tocilizumab in SJIA patients is 95%, and absorption half-life is around 2 days. Patients treated with subcutaneous tocilizumab have a steady-state C_{max} lower than that achieved with IV administration. Steady-state C_{min} and C_{mean} are comparable in patients after subcutaneous or IV dosing across body weights. For doses of 162 mg subcutaneous every week (patients weighing 30 kg or more), estimated median C_{max}, C_{min}, and C_{mean} were 89.8 mcg/mL, 72.4 mcg/mL, and 82.4 mcg/mL, respectively, during pharmacokinetic trials. For doses of 162 mg subcutaneous every 2 weeks (patients weighing less than 30 kg), estimated median C_{max}, C_{min}, and C_{mean} were 127 mcg/mL, 64.2 mcg/mL, and 92.7 mcg/mL, respectively. Steady-state was reached by 12 weeks for both groups.[38283]

- **Geriatric**

Age was not shown to have an effect on the pharmacokinetics of tocilizumab.[38283]

- **Gender Differences**

Gender was not shown to have an effect on the pharmacokinetics of tocilizumab.[38283]

- **Ethnic Differences**

Race was not shown to have an effect on the pharmacokinetics of tocilizumab.[38283]

- **Obesity**

Population analysis identified body weight as a significant covariate impacting the pharmacokinetics of tocilizumab. When given IV on a mg/kg basis, individuals weighing 100 kg or more are predicted to have mean steady-state exposures higher than mean values for the patient population. In RA patients, the body weight-based dose (8 mg per kg) resulted in approximately 86% higher exposure in patients weighing more than 100 kg in comparison to patients who weigh less than 60 kg. Therefore, tocilizumab doses exceeding 800 mg per IV infusion are not recommended in patients with RA. There was an inverse relationship between tocilizumab exposure and body weight for flat dose subcutaneous regimens. Due to the flat dosing employed for subcutaneous administration of tocilizumab, no modifications are necessary by this dosing route.[38283]

In GCA patients, higher exposure was observed in patients with lower body weight. For the 162 mg every week dosing regimen, the steady-state C_{mean} was 51% higher in patients with body weight less than 60 kg compared to patients weighing between 60 to 100 kg. For the 162 mg every other week regimen, the steady-state C_{mean} was 129% higher in patients weighing less than 60 kg compared to patients weighing between 60 to 100 kg. There is limited data for patients above 100 kg (n=7). Due to the flat dosing employed for subcutaneous administration of tocilizumab, no modifications are necessary by this dosing route.[38283]

Revision Date: 03/24/2020 10:09:02 AM

References

38283 – Actemra (tocilizumab) injection package insert. South San Francisco, CA: Genentech, Inc.; 2019 Jun.

Pregnancy/Breast-feeding

Pregnancy

Limited available data are not sufficient to determine whether the use of tocilizumab during human pregnancy is associated with risk for major birth defects or miscarriage. Based on animal data, there may be a potential risk to the fetus. In animal reproduction studies, intravenous administration of tocilizumab to Cynomolgus monkeys during organogenesis resulted in abortion/embryo-fetal death at doses 1.25 times or more of the maximum recommended human dose (MRHD). Monoclonal antibodies, like tocilizumab, are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. This may affect the immune response in the in utero exposed infant; consider risks and benefits before administering live or live-attenuated vaccines to neonates or infants exposed to tocilizumab in utero. A pregnancy registry has been established to monitor maternal and fetal outcomes; health care providers are encouraged to register pregnant women exposed to tocilizumab by calling 1-877-311-8972.[38283] Due to limited data during pregnancy, guidelines state that tocilizumab should be replaced before conception by another medication, if possible. The drug should be used during pregnancy only when no other pregnancy-compatible drug can effectively control the maternal disease.[62180] Tocilizumab may affect labor and obstetric delivery. Inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity, leading to potential delays in parturition.[38283]

Breast-Feeding

The lack of clinical data during lactation precludes clear determination of the risk of tocilizumab to the breast-feeding infant; therefore the developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for tocilizumab and the potential adverse effects on the breastfed child from exposure to the drug or the underlying maternal condition. There is no information available on the presence of tocilizumab in human milk or its effects on the breast-fed infant or milk production. Maternal immunoglobulin G (IgG) is present in human milk. If tocilizumab is transferred into human milk, the effects of local exposure in the gastrointestinal (GI) tract and potential

limited systemic exposure in the infant to tocilizumab are unknown.^[38283] Until more data are available, guidelines state that tocilizumab should generally be avoided during breast-feeding if another therapy is available to control the maternal disease. The drug has a large molecular weight, and experts suggest the oral bioavailability of any drug exposure to the infant through the GI tract is likely low. Breast-feeding should not be discouraged, however, when using the drug if no other options are available.^[62180]

Revision Date: 03/24/2020 10:10:42 AM

References

38283 – Actemra (tocilizumab) injection package insert. South San Francisco, CA: Genentech, Inc.; 2019 Jun.

62180 – Gotestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis.* 2016;75:795-810.

Interactions

Level 2 (Major)

- Abatacept
- Anakinra
- Bacillus Calmette-Guerin Vaccine, BCG
- Baricitinib
- Basiliximab
- Canakinumab
- Daclizumab
- Efalizumab
- Influenza Virus Vaccine
- Intranasal Influenza Vaccine
- Live Vaccines
- Measles Virus; Mumps Virus; Rubella Virus; Varicella Virus Vaccine, Live
- Measles/Mumps/Rubella Vaccines, MMR
- Muromonab-CD3
- Ofatumumab
- Rituximab
- Rituximab; Hyaluronidase
- Rotavirus Vaccine
- Rubella Virus Vaccine Live
- Sarilumab
- Secukinumab
- Smallpox and Monkeypox Vaccine, Live, Nonreplicating
- Smallpox Vaccine, Vaccinia Vaccine
- Tofacitinib
- Tumor Necrosis Factor modifiers
- Typhoid Vaccine
- Upadacitinib
- Ustekinumab
- Varicella-Zoster Virus Vaccine, Live
- Yellow Fever Vaccine, Live

Level 3 (Moderate)

- Alfentanil
- Amlodipine; Atorvastatin
- Apixaban
- Atorvastatin
- Atorvastatin; Ezetimibe
- Belladonna Alkaloids; Ergotamine; Phenobarbital
- Caffeine; Ergotamine
- Carbamazepine
- Cisapride
- Cyclosporine
- Dextromethorphan; Quinidine
- Dihydroergotamine
- Ergotamine
- Ethosuximide
- Everolimus
- Ezetimibe; Simvastatin
- Fentanyl
- Fosphenytoin
- Hydrocortisone
- Lovastatin
- Lovastatin; Niacin
- Niacin; Simvastatin
- Oral Contraceptives
- Phenytoin
- Pimozide
- Quinidine
- Rivaroxaban
- Simvastatin
- Simvastatin; Sitagliptin
- Sirolimus
- Tacrolimus
- Theophylline, Aminophylline
- Thioridazine
- Tizanidine
- Warfarin

Level 4 (Minor)

- Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine
 - Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine
 - Acetaminophen; Dextromethorphan
 - Acetaminophen; Dextromethorphan; Doxylamine
 - Acetaminophen; Dextromethorphan; Guaifenesin; Phenylephrine
 - Acetaminophen; Dextromethorphan; Phenylephrine
 - Acetaminophen; Dextromethorphan; Pseudoephedrine
 - Amoxicillin; Clarithromycin; Omeprazole
 - Aspirin, ASA; Omeprazole
 - Brompheniramine; Dextromethorphan; Guaifenesin
 - Carbinoxamine; Dextromethorphan; Pseudoephedrine
 - Chlorpheniramine; Dextromethorphan
 - Chlorpheniramine; Dextromethorphan; Phenylephrine
 - Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine
 - Dextromethorphan
 - Dextromethorphan; Diphenhydramine; Phenylephrine
 - Dextromethorphan; Guaifenesin
 - Dextromethorphan; Guaifenesin; Phenylephrine
 - Dextromethorphan; Guaifenesin; Potassium Guaiacolsulfonate
 - Dextromethorphan; Guaifenesin; Pseudoephedrine
 - Dextromethorphan; Promethazine
 - Omeprazole
 - Omeprazole; Amoxicillin; Rifabutin
 - Omeprazole; Sodium Bicarbonate
-

Abatacept: (Major) Avoid the concomitant use of tocilizumab with biological DMARDs, including selective costimulation modulators such as abatacept; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [27940] [38283]

Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Acetaminophen; Dextromethorphan: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Acetaminophen; Dextromethorphan; Doxylamine: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single

tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Acetaminophen; Dextromethorphan; Guaifenesin; Phenylephrine: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Acetaminophen; Dextromethorphan; Phenylephrine: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Acetaminophen; Dextromethorphan; Pseudoephedrine: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Alfentanil: (Moderate) Monitor for evidence of reduced effect if alfentanil coadministration with tocilizumab is necessary; alfentanil dosage adjustment may be needed. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as alfentanil, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Alfentanil is a CYP3A4 substrate and narrow therapeutic index drug. [38283]

Amlodipine; Atorvastatin: (Moderate) Utilize caution with concomitant use of tocilizumab and CYP3A4 substrate drugs, such as atorvastatin, where a decrease in effectiveness is undesirable. Monitor lipid panels and adjust therapy as indicated. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 57% decrease in the exposure of another "statin" was noted 1 week after a single tocilizumab dose. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Atorvastatin is a CYP3A4 substrate. [38283]

Amoxicillin; Clarithromycin; Omeprazole: (Minor) Concomitant use of tocilizumab and omeprazole may lead to a decrease in the efficacy of omeprazole. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 12 to 28% decrease in omeprazole exposure occurred 1 week after a single tocilizumab dose. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Omeprazole is a substrate of both CYP2C19 and CYP3A4. [38283]

Anakinra: (Major) Avoid the concomitant use of tocilizumab with biological DMARDs, including interleukin-1 receptor antagonists such as anakinra; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [27940] [38283]

Apixaban: (Moderate) Monitor for a decrease in efficacy of apixaban if used with tocilizumab. Until more data are available, consider using an anticoagulant without dependence on CYP450 enzymes for metabolism (e.g., heparins, edoxaban). The formation of CYP450 enzymes may be suppressed by increased concentrations of cytokines such as IL-6 during chronic inflammation. It is expected that the activity of CYP450 enzymes could increase to normal concentrations during treatment with an IL-6 antagonist such as tocilizumab; these effects on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes [including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4]. Apixaban is a substrate for CYP3A4. [38283] [52739] [65210]

Aspirin, ASA; Omeprazole: (Minor) Concomitant use of tocilizumab and omeprazole may lead to a decrease in the efficacy of omeprazole. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 12 to 28% decrease in omeprazole exposure occurred 1 week after a single tocilizumab dose. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Omeprazole is a substrate of both CYP2C19 and CYP3A4. [38283]

Atorvastatin: (Moderate) Utilize caution with concomitant use of tocilizumab and CYP3A4 substrate drugs, such as atorvastatin, where a decrease in effectiveness is undesirable. Monitor lipid panels and adjust therapy as indicated. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 57% decrease in the exposure of another "statin" was noted 1 week after a single tocilizumab dose. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Atorvastatin is a CYP3A4 substrate. [38283]

Atorvastatin; Ezetimibe: (Moderate) Utilize caution with concomitant use of tocilizumab and CYP3A4 substrate drugs, such as atorvastatin, where a decrease in effectiveness is undesirable. Monitor lipid panels and adjust therapy as indicated. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 57% decrease in the exposure of another "statin" was noted 1 week after a single tocilizumab dose. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Atorvastatin is a CYP3A4 substrate. [38283]

Bacillus Calmette-Guerin Vaccine, BCG: (Major) Avoid concurrent use of live vaccines during treatment with tocilizumab due to potentially increased risk of infections; clinical safety of live vaccines during tocilizumab treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [38283] [51778]

Baricitinib: (Major) Avoid the concomitant use of tocilizumab with other biological DMARDs such as baricitinib; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [38283] [63229]

Basiliximab: (Major) Avoid using tocilizumab with immunosuppressive biological agents such as basiliximab because of the possibility of increased immunosuppression and increased risk of infection. The concurrent use of tocilizumab with other biological agents has not been studied. Most patients taking tocilizumab who developed serious infections were taking concomitant immunosuppressives. [28018] [38283]

Belladonna Alkaloids; Ergotamine; Phenobarbital: (Moderate) Monitor for decreased efficacy of ergotamine if coadministration with tocilizumab is necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as ergotamine, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Ergotamine is a CYP3A4 substrate and narrow therapeutic index drug. [38283]

Brompheniramine; Dextromethorphan; Guaifenesin: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect

on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Caffeine; Ergotamine: (Moderate) Monitor for decreased efficacy of ergotamine if coadministration with tocilizumab is necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as ergotamine, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Ergotamine is a CYP3A4 substrate and narrow therapeutic index drug. [38283]

Canakinumab: (Major) Avoid using tocilizumab with other biological DMARDs including interleukin-1 receptor antagonists such as canakinumab; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [38283]

Carbamazepine: (Moderate) Monitor carbamazepine concentrations and watch for decreased efficacy of carbamazepine if coadministration with tocilizumab is necessary; adjust carbamazepine dosage as necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as carbamazepine, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Carbamazepine is a substrate of both CYP1A2 and CYP3A4 and narrow therapeutic index drug. [38283]

Carbinoxamine; Dextromethorphan; Pseudoephedrine: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Chlorpheniramine; Dextromethorphan: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Chlorpheniramine; Dextromethorphan; Phenylephrine: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Cisapride: (Moderate) Monitor for decreased efficacy of cisapride if coadministration with tocilizumab is necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as cisapride, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for

several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Cisapride is a CYP3A4 substrate and narrow therapeutic index drug. [38283]

Cyclosporine: (Moderate) Monitor cyclosporine levels and adjust the dose of cyclosporine as appropriate if coadministration with tocilizumab is necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as cyclosporine, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Cyclosporine is a CYP3A4 substrate and narrow therapeutic index drug. [38283]

Daclizumab: (Major) Avoid using tocilizumab with biological immunosuppressive agents because of the possibility of increased immunosuppression and increased risk of infection. The concurrent use of tocilizumab with biological DMARDs such as daclizumab has not been studied. Daclizumab is a biologic monoclonal antibody binds specifically to the alpha subunit of the human high-affinity interleukin (IL)-2 receptor, producing immunosuppression. [38283] [60841]

Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrophan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Dextromethorphan: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrophan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Dextromethorphan; Diphenhydramine; Phenylephrine: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrophan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Dextromethorphan; Guaifenesin: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrophan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Dextromethorphan; Guaifenesin; Phenylephrine: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrophan was noted 1 week after a single

tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Dextromethorphan; Guaifenesin; Potassium Guaiacolsulfonate: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Dextromethorphan; Guaifenesin; Pseudoephedrine: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Dextromethorphan; Promethazine: (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Dextromethorphan; Quinidine: (Moderate) Monitor quinidine levels and adjust the dose of quinidine as appropriate if coadministration with tocilizumab is necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as quinidine, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Quinidine is a CYP3A4 substrate and narrow therapeutic index drug. [38283] (Minor) Concomitant use of tocilizumab and dextromethorphan may lead to a decrease in the efficacy of dextromethorphan; clinical significance of this interaction is not known or established. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 5% decrease in dextromethorphan exposure and a 29% decrease in its metabolite, dextrorphan was noted 1 week after a single tocilizumab infusion. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dextromethorphan is a CYP2D6 substrate. [38283] [42280] [56579]

Dihydroergotamine: (Moderate) Monitor for decreased efficacy of dihydroergotamine if coadministration with tocilizumab is necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as dihydroergotamine, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dihydroergotamine is a CYP3A4 substrate and narrow therapeutic index drug. [38283]

Efalizumab: (Major) Avoid using tocilizumab with other biological DMARDs because of the possibility of increased immunosuppression and increased risk of infection. The concurrent use of tocilizumab with biological DMARDs such as efalizumab has not been studied. [38283] [59721]

Ergotamine: (Moderate) Monitor for decreased efficacy of ergotamine if coadministration with tocilizumab is necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as ergotamine, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Ergotamine is a CYP3A4 substrate and narrow therapeutic index drug. [38283]

Ethosuximide: (Moderate) Monitor for reduced efficacy of ethosuximide, monitor drug concentrations, and adjust the dose of ethosuximide as appropriate if coadministration with tocilizumab is necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as ethosuximide, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Ethosuximide is a CYP3A4 substrate and narrow therapeutic index drug. [38283]

Everolimus: (Moderate) Monitor for clinical response in patients taking everolimus concurrently with tocilizumab. For indications where therapeutic drug monitoring is appropriate, monitor everolimus trough concentrations and adjust the dose of everolimus accordingly. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as everolimus, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Everolimus is a CYP3A4 substrate and narrow therapeutic index drug. [38283]

Ezetimibe; Simvastatin: (Moderate) Utilize caution with concomitant use of tocilizumab and CYP3A4 substrate drugs, such as simvastatin, where a decrease in effectiveness is undesirable. Monitor lipid panels and adjust therapy as indicated. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 57% decrease in simvastatin exposure was noted 1 week after a single tocilizumab dose. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Simvastatin is a CYP3A4 substrate. [38283]

Fentanyl: (Moderate) Monitor for evidence of reduced pain control or opioid withdrawal if fentanyl coadministration with tocilizumab is necessary; fentanyl dosage adjustment may be needed. Inhibition of IL-6 signaling by sarilumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as fentanyl, may have fluctuations in drug levels and therapeutic effect when sarilumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping sarilumab. In vitro, sarilumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Fentanyl is a CYP3A4 substrate and narrow therapeutic index drug. [38283]

Fosphenytoin: (Moderate) Monitor drug concentrations and watch for decreased efficacy of fosphenytoin if use with tocilizumab is necessary; adjust fosphenytoin dosage as necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as fosphenytoin, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Fosphenytoin is a substrate of both CYP2C9 and CYP2C19 and narrow therapeutic index drug. [38283]

Hydrocortisone: (Moderate) Closely observe patients for signs of infection. Most patients taking tocilizumab who developed serious infections were taking concomitant immunosuppressives such as systemic corticosteroids. [38283]

Influenza Virus Vaccine: (Major) Avoid concurrent use of live vaccines during treatment with tocilizumab due to potentially increased risk of infections; clinical safety of live vaccines during tocilizumab treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to

patients receiving tocilizumab. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [38283] [51778]

Intranasal Influenza Vaccine: (Major) Avoid concurrent use of live vaccines during treatment with tocilizumab due to potentially increased risk of infections; clinical safety of live vaccines during tocilizumab treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [38283] [51778]

Live Vaccines: (Major) Avoid concurrent use of live vaccines during treatment with tocilizumab due to potentially increased risk of infections; clinical safety of live vaccines during tocilizumab treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [38283] [51778]

Lovastatin: (Moderate) Utilize caution with concomitant use of tocilizumab and CYP3A4 substrate drugs, such as lovastatin, where a decrease in effectiveness is undesirable. Monitor lipid panels and adjust therapy as indicated. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 57% decrease in the exposure of another "statin" was noted 1 week after a single tocilizumab dose. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Lovastatin is a CYP3A4 substrate. [38283]

Lovastatin; Niacin: (Moderate) Utilize caution with concomitant use of tocilizumab and CYP3A4 substrate drugs, such as lovastatin, where a decrease in effectiveness is undesirable. Monitor lipid panels and adjust therapy as indicated. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 57% decrease in the exposure of another "statin" was noted 1 week after a single tocilizumab dose. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Lovastatin is a CYP3A4 substrate. [38283]

Measles Virus; Mumps Virus; Rubella Virus; Varicella Virus Vaccine, Live: (Major) Avoid concurrent use of live vaccines during treatment with tocilizumab due to potentially increased risk of infections; clinical safety of live vaccines during tocilizumab treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [38283] [51778]

Measles/Mumps/Rubella Vaccines, MMR: (Major) Avoid concurrent use of live vaccines during treatment with tocilizumab due to potentially increased risk of infections; clinical safety of live vaccines during tocilizumab treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [38283] [51778]

Muromonab-CD3: (Major) Closely observe patients for signs of infection if immunosuppressive biologic agents such as Muromonab-CD3 are used concomitantly with tocilizumab. The use of tocilizumab with other biologic immunosuppressive agents has not been studied. Most patients taking tocilizumab who developed serious infections were taking concomitant immunosuppressives. [38283] [41935]

Niacin; Simvastatin: (Moderate) Utilize caution with concomitant use of tocilizumab and CYP3A4 substrate drugs, such as simvastatin, where a decrease in effectiveness is undesirable. Monitor lipid panels and adjust therapy as indicated. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 57% decrease in simvastatin exposure was noted 1 week after a single tocilizumab dose. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Simvastatin is a CYP3A4 substrate. [38283]

Ofatumumab: (Major) Avoid the concomitant use of ofatumumab and tocilizumab; coadministration has not been studied and may result in additive immunosuppression and an increased risk of infection. [38283] [45566]

Omeprazole: (Minor) Concomitant use of tocilizumab and omeprazole may lead to a decrease in the efficacy of omeprazole. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 12 to 28% decrease in omeprazole exposure occurred 1 week after a single tocilizumab dose. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Omeprazole is a substrate of both CYP2C19 and CYP3A4. [38283]

Omeprazole; Amoxicillin; Rifabutin: (Minor) Concomitant use of tocilizumab and omeprazole may lead to a decrease in the efficacy of omeprazole. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 12 to 28% decrease in omeprazole exposure occurred 1 week after a single tocilizumab dose. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Omeprazole is a substrate of both CYP2C19 and CYP3A4. [38283]

Omeprazole; Sodium Bicarbonate: (Minor) Concomitant use of tocilizumab and omeprazole may lead to a decrease in the efficacy of omeprazole. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 12 to 28% decrease in omeprazole exposure occurred 1 week after a single tocilizumab dose. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Omeprazole is a substrate of both CYP2C19 and CYP3A4. [38283]

Oral Contraceptives: (Moderate) Utilize caution with concomitant use of tocilizumab and CYP3A4 substrate drugs, such as combined hormonal oral contraceptives, where a decrease in effectiveness is undesirable. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. [38283]

Phenytoin: (Moderate) Monitor phenytoin concentrations and watch for decreased efficacy of phenytoin if coadministration with tocilizumab is necessary; adjust phenytoin dosage as necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as phenytoin, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Phenytoin is a substrate of both CYP2C9 and CYP2C19 and narrow therapeutic index drug. [38283]

Pimozide: (Moderate) Monitor for an altered patient response to pimozide if coadministration with tocilizumab is necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as pimozide, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Pimozide is a substrate of both CYP2D6 and CYP3A4 and narrow therapeutic index drug. [38283]

Quinidine: (Moderate) Monitor quinidine levels and adjust the dose of quinidine as appropriate if coadministration with tocilizumab is necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as quinidine, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Quinidine is a CYP3A4 substrate and narrow therapeutic index drug. [38283]

Rituximab: (Major) Avoid the concomitant use of rituximab and tocilizumab; coadministration has not been studied and may result in additive immunosuppression and an increased risk of infection. [38283] [49773]

Rituximab; Hyaluronidase: (Major) Avoid the concomitant use of rituximab and tocilizumab; coadministration has not been studied and may result in additive immunosuppression and an increased risk of infection. [38283] [49773]

Rivaroxaban: (Moderate) Monitor for a decrease in efficacy of rivaroxaban if used with tocilizumab. Until more data are available, consider using an anticoagulant without dependence on CYP450 enzymes for metabolism (e.g., heparins, edoxaban). The formation of CYP450 enzymes may be suppressed by increased concentrations of cytokines such as IL-6 during chronic inflammation. It is expected that the activity of CYP450 enzymes could increase to normal concentrations during treatment with an IL-6 antagonist such as tocilizumab; these effects on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes [including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4]. Rivaroxaban is a substrate for CYP3A4/5. [38283] [44854] [65210]

Rotavirus Vaccine: (Major) Avoid concurrent use of live vaccines during treatment with tocilizumab due to potentially increased risk of infections; clinical safety of live vaccines during tocilizumab treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [38283] [51778]

Rubella Virus Vaccine Live: (Major) Avoid concurrent use of live vaccines during treatment with tocilizumab due to potentially increased risk of infections; clinical safety of live vaccines during tocilizumab treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [38283] [51778]

Sarilumab: (Major) Avoid using sarilumab with other biological DMARDs, such as tocilizumab; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [38283] [61976]

Secukinumab: (Major) Avoid using tocilizumab with other biological DMARDs, such as secukinumab; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [38283]

Simvastatin: (Moderate) Utilize caution with concomitant use of tocilizumab and CYP3A4 substrate drugs, such as simvastatin, where a decrease in effectiveness is undesirable. Monitor lipid panels and adjust therapy as indicated. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 57% decrease in simvastatin exposure was noted 1 week after a single tocilizumab dose. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Simvastatin is a CYP3A4 substrate. [38283]

Simvastatin; Sitagliptin: (Moderate) Utilize caution with concomitant use of tocilizumab and CYP3A4 substrate drugs, such as simvastatin, where a decrease in effectiveness is undesirable. Monitor lipid panels and adjust therapy as indicated. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. A 57% decrease in simvastatin exposure was noted 1 week after a single tocilizumab dose. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Simvastatin is a CYP3A4 substrate. [38283]

Sirolimus: (Moderate) Monitor sirolimus levels and adjust the dose of sirolimus as appropriate if coadministration with tocilizumab is necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as sirolimus, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Sirolimus is a CYP3A4 substrate and narrow therapeutic index drug. [38283]

Smallpox and Monkeypox Vaccine, Live, Nonreplicating: (Major) Avoid concurrent use of live vaccines during treatment with tocilizumab due to potentially increased risk of infections; clinical safety of live vaccines during tocilizumab treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [38283] [51778]

Smallpox Vaccine, Vaccinia Vaccine: (Major) Avoid concurrent use of live vaccines during treatment with tocilizumab due to potentially increased risk of infections; clinical safety of live vaccines during tocilizumab

treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [38283] [51778]

Tacrolimus: (Moderate) Monitor tacrolimus levels and adjust the dose of tacrolimus as appropriate if coadministration with tocilizumab is necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as tacrolimus, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Tacrolimus is a CYP3A4 substrate and narrow therapeutic index drug. [38283]

Theophylline, Aminophylline: (Moderate) Monitor drug concentrations and watch for decreased efficacy of aminophylline or theophylline if coadministration with tocilizumab is necessary; a dosage increase of these methylxanthines may be necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Aminophylline and Theophylline are CYP1A2 substrates and narrow therapeutic index drugs. [38283]

Thioridazine: (Moderate) Monitor for an altered patient response to thioridazine if coadministration with tocilizumab is necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as thioridazine, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Thioridazine is a CYP2D6 substrate and narrow therapeutic index drug. [38283]

Tizanidine: (Moderate) Monitor for reduced efficacy of tizanidine if coadministered with tocilizumab. An adjustment of tizanidine dose may be required. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as tizanidine, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. In vitro, tocilizumab has the potential to affect expression of multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Tizanidine is a CYP1A2 substrate and narrow therapeutic index drug. [38283]

Tofacitinib: (Major) Avoid the concomitant use of tocilizumab with other biological DMARDs such as tofacitinib; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [38283] [52315]

Tumor Necrosis Factor modifiers: (Major) Avoid the concomitant use of tocilizumab with biological DMARDs, such as tumor necrosis factor (TNF) modifiers; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [38283]

Typhoid Vaccine: (Major) Avoid concurrent use of live vaccines during treatment with tocilizumab due to potentially increased risk of infections; clinical safety of live vaccines during tocilizumab treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [38283] [51778]

Upadacitinib: (Major) Avoid the concomitant use of tocilizumab with other biological DMARDs such as upadacitinib; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [38283] [64572]

Ustekinumab: (Major) Avoid the concomitant use of tocilizumab with other biological DMARDs such as ustekinumab; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [38283]

Varicella-Zoster Virus Vaccine, Live: (Major) Avoid concurrent use of live vaccines during treatment with tocilizumab due to potentially increased risk of infections; clinical safety of live vaccines during tocilizumab treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [38283] [51778]

Warfarin: (Moderate) Monitor the INR if tocilizumab is coadministered with warfarin due to the potential for decreased warfarin efficacy; adjust the dose of warfarin as necessary. Inhibition of IL-6 signaling by tocilizumab may restore CYP450 activities to higher levels leading to increased metabolism of drugs that are CYP450 substrates as compared to metabolism prior to treatment. Therefore, CYP450 substrates with a narrow therapeutic index, such as warfarin, may have fluctuations in drug levels and therapeutic effect when tocilizumab therapy is started or discontinued. This effect on CYP450 enzyme activity may persist for several weeks after stopping tocilizumab. [28549] [38283]

Yellow Fever Vaccine, Live: (Major) Avoid concurrent use of live vaccines during treatment with tocilizumab due to potentially increased risk of infections; clinical safety of live vaccines during tocilizumab treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [38283] [51778]

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Monitoring Parameters

- CBC with differential
- LFTs
- platelet count
- serum lipid profile

IV Compatibility of Tocilizumab with:

Legend

-  = Compatible
-  = Incompatible
-  = Results uncertain, variable or dependent on conditions
- ND = No Data Available

From Trissel's 2TM Clinical Pharmaceutics Database 

	Admixture	Syringe	Y-Site Administration	For Dilution
Normal saline- Sodium chloride 0.9%	ND	ND	ND	
Sodium chloride 0.45%	ND	ND	ND	

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US Drug Names

- Actemra

Global Drug names

Argentina

- Actemra - (Roche)

Australia

- Actemra - (Roche)

Austria

- RoActemra - (Roche)

Belgium

- RoActemra - (Roche)

Brazil

- Actemra - (Roche)

Canada

- Actemra - (Roche)

Chile

- Actemra - (Roche)

China

- Actemra - (Roche)

Czech Republic

- RoActemra - (Roche)

Denmark

- RoActemra - (Roche)

Finland

- RoActemra - (Roche)

France

- RoActemra - (Roche)

Germany

- RoActemra - (Chugai)

Greece

- RoActemra - (Roche)

Hong Kong

- Actemra - (Roche)

Hungary

- RoActemra - (Roche)

Indonesia

- Actemra - (Roche)

Ireland

- RoActemra - (Roche)

Israel

- Actemra - (Roche)

Japan

- Actemra - (Chugai)

Malaysia

- Actemra - (Roche)

Mexico

- RoActemra - (Roche)

Netherlands

- RoActemra - (Roche)

New Zealand

- Actemra - (Roche)

Norway

- RoActemra - (Roche)

Philippines

- Actemra - (Roche)

Poland

- RoActemra - (Roche)

Portugal

- RoActemra - (Roche)

Russian Federation

- Actemra - (Roche)

Singapore

- Actemra - (Chugai)

South Africa

- Actemra - (Roche)

Spain

- RoActemra - (Roche)

Sweden

- RoActemra - (Roche)

Switzerland

- Actemra - (Roche)

Thailand

- Actemra - (Roche)

Turkey

- Actemra - (Roche)

Ukraine

- Actemra - (Roche)

United Kingdom

- RoActemra - (Roche)