

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TOFIDENCE safely and effectively. See full prescribing information for TOFIDENCE.

TOFIDENCE™ (tocilizumab-bavi) injection, for intravenous use

Initial U.S. Approval: 2023

TOFIDENCE (tocilizumab-bavi) is biosimilar* to ACTEMRA (tocilizumab).

WARNING: RISK OF SERIOUS INFECTIONS

See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving tocilizumab products. (5.1)
- If a serious infection develops, interrupt TOFIDENCE until the infection is controlled. (5.1)
- Perform test for latent TB; if positive, start treatment for TB prior to starting TOFIDENCE. (5.1)
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)

INDICATIONS AND USAGE

TOFIDENCE™ (tocilizumab-bavi) is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of:

Rheumatoid Arthritis (RA) (1.1)

- Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

Polyarticular Juvenile Idiopathic Arthritis (PJIA) (1.2)

- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.

Systemic Juvenile Idiopathic Arthritis (SJIA) (1.3)

- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

DOSAGE AND ADMINISTRATION

For RA, pJIA and sJIA, TOFIDENCE may be used alone or in combination with methotrexate; and in RA, other DMARDs may be used. (2)

General Dosing Information (2.1)

- It is recommended that TOFIDENCE not be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm³, platelet count below 100,000 per mm³, or who have ALT or AST above 1.5 times the upper limit of normal (ULN). (5.3, 5.4)
- In RA patients, TOFIDENCE doses exceeding 800 mg per infusion are not recommended. (2.2, 12.3)

Rheumatoid Arthritis (2.2)

Recommended Adult Intravenous Dosage:

When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.

Polyarticular Juvenile Idiopathic Arthritis (2.3)

Recommended Intravenous PJIA Dosage Every 4 Weeks	
Patients less than 30 kg weight	10 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Systemic Juvenile Idiopathic Arthritis (2.4)

Recommended Intravenous SJIA Dosage Every 2 Weeks	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Administration of Intravenous Formulation (2.5)

- For adults with RA, PJIA and SJIA patients at or above 30 kg, dilute to 100 mL in 0.9% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique.
- For PJIA and SJIA patients less than 30 kg, dilute to 50 mL in 0.9% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique.
- Administer as a single intravenous drip infusion over 1 hour; do not administer as bolus or push.

Dose Modifications (2.6)

- Recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia.

DOSAGE FORMS AND STRENGTHS

Intravenous Infusion

Injection: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to intravenous infusion (3)

CONTRAINDICATIONS

- TOFIDENCE is contraindicated in patients with known hypersensitivity to tocilizumab products. (4)

WARNINGS AND PRECAUTIONS

- Serious Infections – do not administer TOFIDENCE during an active infection, including localized infections. If a serious infection develops, interrupt TOFIDENCE until the infection is controlled. (5.1)
- Gastrointestinal (GI) perforation—use with caution in patients who may be at increased risk. (5.2)
- Hepatotoxicity- Monitor patients for signs and symptoms of hepatic injury. Modify or discontinue TOFIDENCE if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop. (2.6, 5.3)
- Laboratory monitoring—recommended due to potential consequences of treatment-related changes in neutrophils, platelets, lipids, and liver function tests. (2.6, 5.4)
- Hypersensitivity reactions, including anaphylaxis and death have occurred. (5.6)
- Live vaccines—Avoid use with TOFIDENCE. (5.9, 7.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence of at least 5%): upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen MA Inc. at 1-866-633-4636 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Based on animal data, may cause fetal harm. (8.1)
- **Lactation:** Discontinue drug or nursing taking into consideration importance of drug to mother. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

* Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of TOFIDENCE has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: 9/2023

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with tocilizumab products including TOFIDENCE are at increased risk for developing serious infections that may lead to hospitalization or death [see *Warnings and Precautions (5.1)*, *Adverse Reactions (6.1)*]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt TOFIDENCE until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before TOFIDENCE use and during therapy. Treatment for latent infection should be initiated prior to TOFIDENCE use.**
- **Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with TOFIDENCE should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with TOFIDENCE, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy [see *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis (RA)

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

1.2 Polyarticular Juvenile Idiopathic Arthritis (PJIA)

TOFIDENCE™ (tocilizumab-bavi) is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

1.3 Systemic Juvenile Idiopathic Arthritis (SJIA)

TOFIDENCE™ (tocilizumab-bavi) is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations for Administration

Not Recommended for Concomitant Use with Biological DMARDs

Tocilizumab products have not been studied in combination with biological DMARDs such as TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators because of the possibility of increased immunosuppression and increased risk of infection. Avoid using TOFIDENCE with biological DMARDs.

Baseline Laboratory Evaluation Prior to Treatment

Obtain and assess baseline complete blood count (CBC) and liver function tests prior to treatment.

- RA, PJIA and SJIA – It is recommended that TOFIDENCE not be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm³, platelet count below 100,000 per mm³, or ALT or AST above 1.5 times the upper limit of normal (ULN) [*see Warnings and Precautions (5.3, 5.4)*].

2.2 Recommended Dosage for Rheumatoid Arthritis

TOFIDENCE may be used as monotherapy or concomitantly with methotrexate or other non-biologic DMARDs as an intravenous infusion.

Recommended Intravenous Dosage Regimen:

The recommended dosage of TOFIDENCE for adult patients given as a 60-minute single intravenous drip infusion is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.

- Reduction of dose from 8 mg per kg to 4 mg per kg is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia [*see Dosage and Administration (2.6), Warnings and Precautions (5.3, 5.4), and Adverse Reactions (6.1)*].
- Doses exceeding 800 mg per infusion are not recommended in RA patients [*see Clinical Pharmacology (12.3)*].

When transitioning from intravenous therapy with TOFIDENCE to subcutaneous therapy with another tocilizumab product, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Interruption of dose is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia [see *Dosage and Administration (2.6)* and *Warnings and Precautions (5.3, 5.4)*].

2.3 Recommended Dosage for Polyarticular Juvenile Idiopathic Arthritis

TOFIDENCE may be used as an intravenous infusion alone or in combination with methotrexate. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate.

Recommended Intravenous Dosage Regimen:

The recommended dosage of TOFIDENCE for PJIA patients given once every 4 weeks as a 60-minute single intravenous drip infusion is:

Recommended Intravenous PJIA Dosage Every 4 Weeks	
Patients less than 30 kg weight	10 mg per kg
Patients at or above 30 kg weight	8 mg per kg

When transitioning from intravenous therapy with TOFIDENCE to subcutaneous therapy with another tocilizumab product, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia [see *Dosage and Administration (2.6)*].

2.4 Recommended Dosage for Systemic Juvenile Idiopathic Arthritis

TOFIDENCE may be used as an intravenous infusion or in combination with methotrexate. Do not change a dose based solely on a single visit body weight measurement, as weight may fluctuate.

Recommended Intravenous Dosage Regimen:

The recommended dose of TOFIDENCE for SJIA patients given once every 2 weeks as a 60-minute single intravenous drip infusion is:

Recommended Intravenous SJIA Dosage Every 2 Weeks	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg

When transitioning from intravenous therapy with TOFIDENCE to subcutaneous therapy with another tocilizumab product, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia [see *Dosage and Administration (2.6)*].

2.5 Preparation and Administration Instructions for Intravenous Infusion

TOFIDENCE for intravenous infusion should be diluted by a healthcare professional using aseptic technique as follows:

- Use a sterile needle and syringe to prepare TOFIDENCE.
- Patients **less than 30 kg**: use a **50 mL** infusion bag or bottle of 0.9% Sodium Chloride Injection, USP, and then follow steps 1 and 2 below.
- Patients **at or above 30 kg weight**: use a **100 mL** infusion bag or bottle, and then follow steps 1 and 2 below.
- Step 1. Withdraw a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of the TOFIDENCE injection required for the patient's dose from the infusion bag or bottle [see *Dosage and Administration (2.2, 2.3, 2.4)*].

For Intravenous Use: Volume of TOFIDENCE Injection per kg of Body Weight		
Dosage	Indication	Volume of TOFIDENCE injection per kg of body weight
4 mg/kg	Adult RA	0.2 mL/kg
8 mg/kg	Adult RA, SJIA and PJIA (greater than or equal to 30 kg of body weight)	0.4 mL/kg
10 mg/kg	PJIA (less than 30 kg of body weight)	0.5 mL/kg
12 mg/kg	SJIA (less than 30 kg of body weight)	0.6 mL/kg

- Step 2. Withdraw the amount of TOFIDENCE for intravenous infusion from the vial(s) and add slowly into the 0.9% Sodium Chloride Injection, USP infusion bag or bottle. To mix the solution, gently invert the bag to avoid foaming.
- The fully diluted TOFIDENCE solutions for infusion using 0.9% Sodium Chloride Injection, USP may be stored refrigerated at 36°F to 46°F (2°C to 8°C) for up to 24 hours or room temperature at 68°F to 77°F (20°C to 25°C) for up to 12 hours and should be protected from light.
- TOFIDENCE solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used.
- Allow the fully diluted TOFIDENCE solution to reach room temperature prior to infusion.
- The infusion should be administered over 60 minutes, and must be administered with an infusion set. Do not administer as an intravenous push or bolus.
- TOFIDENCE should not be infused concomitantly in the same intravenous line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of TOFIDENCE with other drugs.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulates and discolorations are noted, the product should not be used.
- Fully diluted TOFIDENCE solutions are compatible with infusion bags and/or infusion sets with the following materials: polypropylene, polyethylene, polyolefin, polyvinyl chloride, polyethersulfone, polyurethane, nylon and stainless steel.

2.6 Dosage Modifications due to Serious Infections or Laboratory Abnormalities

Serious Infections

Hold TOFIDENCE treatment if a patient develops a serious infection until the infection is controlled.

Laboratory Abnormalities

Rheumatoid Arthritis

Liver Enzyme Abnormalities [see <i>Warnings and Precautions (5.3, 5.4)</i>]	
Lab Value	Recommendation for RA
Greater than 1 to 3x ULN	Dose modify concomitant DMARDs if appropriate. For persistent increases in this range: <ul style="list-style-type: none"> • For patients receiving intravenous TOFIDENCE, reduce dose to 4 mg per kg or hold TOFIDENCE until ALT or AST have normalized.
Greater than 3 to 5x ULN (confirmed by repeat testing)	Hold TOFIDENCE dosing until less than 3x ULN and follow recommendations above for greater than 1 to 3x ULN. For persistent increases greater than 3x ULN, discontinue TOFIDENCE.
Greater than 5x ULN	Discontinue TOFIDENCE.

Low Absolute Neutrophil Count (ANC) [see <i>Warnings and Precautions (5.4)</i>]	
Lab Value (cells per mm³)	Recommendation for RA
ANC greater than 1000	Maintain dose.
ANC 500 to 1000	Hold TOFIDENCE dosing. When ANC is greater than 1000 cells per mm ³ : <ul style="list-style-type: none"> • For patients receiving intravenous TOFIDENCE, resume TOFIDENCE at 4 mg per kg and increase to 8 mg per kg as clinically appropriate.
ANC less than 500	Discontinue TOFIDENCE.

Low Platelet Count [see <i>Warnings and Precautions (5.4)</i>]	
Lab Value (cells per mm³)	Recommendation for RA

50,000 to 100,000	Hold TOFIDENCE dosing. When platelet count is greater than 100,000 cells per mm ³ : <ul style="list-style-type: none">For patients receiving intravenous TOFIDENCE, resume TOFIDENCE at 4 mg per kg and increase to 8 mg per kg as clinically appropriate.
Less than 50,000	Discontinue TOFIDENCE.

Polyarticular and Systemic Juvenile Idiopathic Arthritis

Dose reduction of tocilizumab products has not been studied in the PJIA and SJIA populations. Dose interruptions of TOFIDENCE are recommended for liver enzyme abnormalities, low neutrophil counts, and low platelet counts in patients with PJIA and SJIA at levels similar to what is outlined above for patients with RA. If appropriate, dose modify or stop concomitant methotrexate and/or other medications and hold TOFIDENCE dosing until the clinical situation has been evaluated. In PJIA and SJIA the decision to discontinue TOFIDENCE for a laboratory abnormality should be based upon the medical assessment of the individual patient.

3 DOSAGE FORMS AND STRENGTHS

Intravenous Infusion

Injection: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL as a clear to opalescent, colorless to light yellow solution in 20 mg/mL single-dose vials for further dilution prior to intravenous infusion.

4 CONTRAINDICATIONS

TOFIDENCE is contraindicated in patients with known hypersensitivity to tocilizumab products [see *Warnings and Precautions (5.6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious 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 products. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis [see *Adverse Reactions (6.1)*]. Among opportunistic infections, tuberculosis, cryptococcus, aspergillosis, candidiasis, and pneumocystosis were reported with tocilizumab products. Other serious infections, not reported in clinical studies, may also occur (e.g., histoplasmosis, coccidioidomycosis, listeriosis). Patients have presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids which in addition to rheumatoid arthritis may predispose them to infections.

Do not administer TOFIDENCE in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating TOFIDENCE in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of serious or an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with TOFIDENCE, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants [see *Dosage and Administration (2.1)*, *Adverse Reactions (6.1)*, and *Patient Counseling Information (17)*].

Hold TOFIDENCE if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with TOFIDENCE should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, initiate appropriate antimicrobial therapy, and closely monitor the patient.

Tuberculosis

Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating TOFIDENCE.

Consider anti-tuberculosis therapy prior to initiation of TOFIDENCE in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having 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.

Closely monitor patients for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

The incidence of tuberculosis in worldwide clinical development programs is 0.1%. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before initiating TOFIDENCE.

Viral Reactivation

Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster exacerbation were observed in clinical studies with tocilizumab. No cases of Hepatitis B reactivation were observed in the trials; however patients who screened positive for hepatitis were excluded.

5.2 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials, primarily as complications of diverticulitis in patients treated with tocilizumab. Use TOFIDENCE with caution in patients who may be at increased risk for gastrointestinal perforation. Promptly evaluate patients presenting with new onset abdominal symptoms for early identification of gastrointestinal perforation [*see Adverse Reactions (6.1)*].

5.3 Hepatotoxicity

Serious cases of hepatic injury have been observed in patients taking intravenous tocilizumab products. Some of these cases have resulted in liver transplant or death. Time to onset for cases ranged from months to years after treatment initiation with tocilizumab products. While most cases presented with marked elevations of transaminases (> 5 times ULN), some cases presented with signs or symptoms of liver dysfunction and only mildly elevated transaminases.

During randomized controlled studies, treatment with tocilizumab was associated with a higher incidence of transaminase elevations [*see Adverse Reactions (6.1, 6.2, 6.3)*]. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with tocilizumab.

For RA patients, obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) before initiating TOFIDENCE, every 4 to 8 weeks after start of therapy for the first 6 months of treatment and every 3 months thereafter. It is not recommended to initiate TOFIDENCE treatment in RA patients with elevated transaminases ALT or AST greater than 1.5x ULN. In patients who develop elevated ALT or AST greater than 5x ULN, discontinue TOFIDENCE. For recommended modifications based upon increase in transaminases *see Dosage and Administration (2.6)*.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, such as fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (e.g., ALT greater than three times the upper limit of the reference range, serum total bilirubin greater than two times the upper limit of the reference range), TOFIDENCE treatment should be interrupted and investigation done to establish the probable cause. TOFIDENCE should only be restarted in patients with another explanation for the liver test abnormalities after normalization of the liver tests.

A similar pattern of liver enzyme elevation is noted with tocilizumab products treatment in the PJIA and SJIA populations. Monitor liver test panel at the time of the second administration and thereafter every 4 to 8 weeks for PJIA and every 2 to 4 weeks for SJIA.

5.4 Changes in Laboratory Parameters

Patients with Rheumatoid Arthritis

Neutropenia

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

– It is not recommended to initiate TOFIDENCE treatment in RA patients with a low neutrophil count, i.e., absolute neutrophil count (ANC) less than 2000 per mm³. In patients who develop an absolute neutrophil count less than 500 per mm³ treatment is not recommended.

– Monitor neutrophils 4 to 8 weeks after start of therapy and every 3 months thereafter [see *Clinical Pharmacology (12.2)*]. For recommended modifications based on ANC results see *Dosage and Administration (2.6)*.

Thrombocytopenia

Treatment with tocilizumab products was associated with a reduction in platelet counts. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials [see *Adverse Reactions (6.1)*].

– It is not recommended to initiate TOFIDENCE treatment in RA patients with a platelet count below 100,000 per mm³. In patients who develop a platelet count less than 50,000 per mm³ treatment is not recommended.

– Monitor platelets 4 to 8 weeks after start of therapy and every 3 months thereafter. For recommended modifications based on platelet counts see *Dosage and Administration (2.6)*.

Elevated Liver Enzymes

Refer to 5.3 Hepatotoxicity. For recommended modifications see *Dosage and Administration (2.6)*.

Lipid Abnormalities

Treatment with tocilizumab products was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol [see *Adverse Reactions (6.1)*].

– Assess lipid parameters approximately 4 to 8 weeks following initiation of TOFIDENCE therapy.

– Subsequently, manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

Patients with Polyarticular and Systemic Juvenile Idiopathic Arthritis

A similar pattern of liver enzyme elevation, low neutrophil count, low platelet count and lipid elevations is noted with tocilizumab products treatment in the PJIA and SJIA populations.

Monitor neutrophils, platelets, ALT and AST at the time of the second administration and thereafter every 4 to 8 weeks for PJIA and every 2 to 4 weeks for SJIA. Monitor lipids as above for approved adult indications [see *Dosage and Administration (2.6)*].

5.5 Immunosuppression

The impact of treatment with tocilizumab products on the development of malignancies is not known but malignancies were observed in clinical studies [see *Adverse Reactions (6.1)*]. TOFIDENCE is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.

5.6 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in association with tocilizumab products [see *Adverse Reactions (6)*] and anaphylactic events with a fatal outcome have been reported with intravenous infusion of tocilizumab products. Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials of intravenous tocilizumab and 0.2% (8 out of 4009) of patients in the intravenous all-exposure RA population. In the SJIA controlled trial with intravenous tocilizumab, 1 out of 112 patients (0.9%) experienced hypersensitivity reactions that required treatment discontinuation. In the PJIA controlled trial with intravenous tocilizumab 0 out of 188 patients (0%) in the tocilizumab all-exposure population experienced hypersensitivity reactions that required treatment discontinuation. Reactions that required treatment discontinuation included generalized erythema, rash, and urticaria. Injection site reactions were categorized separately [see *Adverse Reactions (6)*].

In the postmarketing setting, events of hypersensitivity reactions, including anaphylaxis and death have occurred in patients treated with a range of doses of intravenous tocilizumab products, with or without concomitant therapies. Events have occurred in patients who received premedication. Hypersensitivity, including anaphylaxis events, have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of tocilizumab products [see *Adverse Reactions (6.3)*]. TOFIDENCE for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of TOFIDENCE immediately and discontinue TOFIDENCE permanently. Do not administer TOFIDENCE to patients with known hypersensitivity to tocilizumab products [see *Contraindications (4)* and *Adverse Reactions (6)*].

5.7 Demyelinating Disorders

The impact of treatment with tocilizumab products on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in RA clinical studies. Monitor patients for signs and symptoms potentially indicative of

demyelinating disorders. Prescribers should exercise caution in considering the use of TOFIDENCE in patients with preexisting or recent onset demyelinating disorders.

5.8 Active Hepatic Disease and Hepatic Impairment

Treatment with TOFIDENCE is not recommended in patients with active hepatic disease or hepatic impairment [see *Adverse Reactions (6.1)*, *Use in Specific Populations (8.6)*].

5.9 Vaccinations

Avoid use of live vaccines concurrently with TOFIDENCE 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 products.

No data are available on the effectiveness of vaccination in patients receiving tocilizumab products. Because IL-6 inhibition may interfere with the normal immune response to new antigens, it is recommended that all patients, particularly pediatric or elderly patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating TOFIDENCE therapy. The interval between live vaccinations and initiation of TOFIDENCE therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Serious Infections [see *Warnings and Precautions (5.1)*]
- Gastrointestinal Perforations [see *Warnings and Precautions (5.2)*]
- Laboratory Parameters [see *Warnings and Precautions (5.4)*]
- Immunosuppression [see *Warnings and Precautions (5.5)*]
- Hypersensitivity Reactions, Including Anaphylaxis [see *Warnings and Precautions (5.6)*]
- Demyelinating Disorders [see *Warnings and Precautions (5.7)*]
- Active Hepatic Disease and Hepatic Impairment [see *Warnings and Precautions (5.8)*]

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

6.1 Clinical Trials Experience in Rheumatoid Arthritis Patients Treated with Intravenous Tocilizumab (Tocilizumab-IV)

The tocilizumab-IV data in rheumatoid arthritis (RA) includes 5 double-blind, controlled, multicenter studies. In these studies, patients received doses of tocilizumab-IV 8 mg per kg monotherapy (288 patients), tocilizumab-IV 8 mg per kg in combination with DMARDs

(including methotrexate) (1582 patients), or tocilizumab-IV 4 mg per kg in combination with methotrexate (774 patients).

The all exposure population includes all patients in registration studies who received at least one dose of tocilizumab-IV. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3309 for at least one year; 2954 received treatment for at least 2 years and 2189 for 3 years.

All patients in these studies had moderately to severely active rheumatoid arthritis. The study population had a mean age of 52 years, 82% were female and 74% were Caucasian.

The most common serious adverse reactions were serious infections [see *Warnings and Precautions (5.1)*]. The most commonly reported adverse reactions in controlled studies up to 24 weeks (occurring in at least 5% of patients treated with tocilizumab-IV monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The proportion of patients who discontinued treatment due to any adverse reactions during the double-blind, placebo-controlled studies was 5% for patients taking tocilizumab-IV and 3% for placebo-treated patients. The most common adverse reactions that required discontinuation of tocilizumab-IV were increased hepatic transaminase values (per protocol requirement) and serious infections.

Overall Infections

In the 24 week, controlled clinical studies, the rate of infections in the tocilizumab-IV monotherapy group was 119 events per 100 patient-years and was similar in the methotrexate monotherapy group. The rate of infections in the 4 mg per kg and 8 mg per kg tocilizumab-IV plus DMARD group was 133 and 127 events per 100 patient-years, respectively, compared to 112 events per 100 patient-years in the placebo plus DMARD group. The most commonly reported infections (5% to 8% of patients) were upper respiratory tract infections and nasopharyngitis.

The overall rate of infections with tocilizumab-IV in the all exposure population remained consistent with rates in the controlled periods of the studies.

Serious Infections

In the 24 week, controlled clinical studies, the rate of serious infections in the tocilizumab-IV monotherapy group was 3.6 per 100 patient-years compared to 1.5 per 100 patient-years in the methotrexate group. The rate of serious infections in the 4 mg per kg and 8 mg per kg tocilizumab-IV plus DMARD group was 4.4 and 5.3 events per 100 patient-years, respectively, compared to 3.9 events per 100 patient-years in the placebo plus DMARD group.

In the all-exposure population, the overall rate of serious infections remained consistent with rates in the controlled periods of the studies. The most common serious infections included

pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported [see *Warnings and Precautions (5.1)*].

In the cardiovascular outcomes Study WA25204, the rate of serious infections in the tocilizumab 8 mg/kg IV every 4 weeks group, with or without DMARD, was 4.5 per 100 patient-years, and the rate in the etanercept 50 mg weekly SC group, with or without DMARD, was 3.2 per 100 patient-years [see *Clinical Studies (14.1)*].

Gastrointestinal Perforations

During the 24 week, controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient-years with tocilizumab-IV therapy.

In the all-exposure population, the overall rate of gastrointestinal perforation remained consistent with rates in the controlled periods of the studies. Reports of gastrointestinal perforation were primarily reported as complications of diverticulitis including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids, or methotrexate [see *Warnings and Precautions (5.2)*]. The relative contribution of these concomitant medications versus tocilizumab-IV to the development of GI perforations is not known.

Infusion Reactions

In the 24 week, controlled clinical studies, adverse events associated with the infusion (occurring during or within 24 hours of the start of infusion) were reported in 8% and 7% of patients in the 4 mg per kg and 8 mg per kg tocilizumab-IV plus DMARD group, respectively, compared to 5% of patients in the placebo plus DMARD group. The most frequently reported event on the 4 mg per kg and 8 mg per kg dose during the infusion was hypertension (1% for both doses), while the most frequently reported event occurring within 24 hours of finishing an infusion were headache (1% for both doses) and skin reactions (1% for both doses), including rash, pruritus and urticaria. These events were not treatment limiting.

Anaphylaxis

Hypersensitivity reactions requiring treatment discontinuation, including anaphylaxis, associated with tocilizumab-IV were reported in 0.1% (3 out of 2644) in the 24 week, controlled trials and in 0.2% (8 out of 4009) in the all-exposure population. These reactions were generally observed during the second to fourth infusion of tocilizumab-IV. Appropriate medical treatment should be available for immediate use in the event of a serious hypersensitivity reaction [see *Warnings and Precautions (5.6)*].

Laboratory Abnormalities

Neutropenia

In the 24 week, controlled clinical studies, decreases in neutrophil counts below 1000 per mm³ occurred in 1.8% and 3.4% of patients in the 4 mg per kg and 8 mg per kg tocilizumab-IV plus DMARD group, respectively, compared to 0.1% of patients in the placebo plus DMARD group. Approximately half of the instances of ANC below 1000 per mm³ occurred within 8 weeks of starting therapy. Decreases in neutrophil counts below 500 per mm³ occurred in 0.4% and 0.3% of patients in the 4 mg per kg and 8 mg per kg tocilizumab-IV plus DMARD, respectively, compared to 0.1% of patients in the placebo plus DMARD group. There was no clear relationship between decreases in neutrophils below 1000 per mm³ and the occurrence of serious infections.

In the all-exposure population, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 24 week controlled clinical studies [see *Warnings and Precautions (5.4)*].

Thrombocytopenia

In the 24 week, controlled clinical studies, decreases in platelet counts below 100,000 per mm³ occurred in 1.3% and 1.7% of patients on 4 mg per kg and 8 mg per kg tocilizumab-IV plus DMARD, respectively, compared to 0.5% of patients on placebo plus DMARD, without associated bleeding events.

In the all-exposure population, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 24 week controlled clinical studies [see *Warnings and Precautions (5.4)*].

Elevated Liver Enzymes

Liver enzyme abnormalities are summarized in [Table 1](#). In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of tocilizumab-IV, or reduction in tocilizumab-IV dose, resulted in decrease or normalization of liver enzymes [see *Dosage and Administration (2.6)*]. These elevations were not associated with clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency [see *Warnings and Precautions (5.3, 5.4)*].

Table 1 Incidence of Liver Enzyme Abnormalities in the 24 Week Controlled Period of Studies I to V*

	Tocilizumab 8 mg per kg MONOTHER APY	Methotrexate	Tocilizumab 4 mg per kg + DMARDs	Tocilizumab 8 mg per kg + DMARDs	Placebo + DMARDs
	N = 288 (%)	N = 284 (%)	N = 774 (%)	N = 1582 (%)	N = 1170 (%)
AST (U/L)					
> ULN to 3× ULN	22	26	34	41	17
> 3× ULN to 5× ULN	0.3	2	1	2	0.3
> 5× ULN	0.7	0.4	0.1	0.2	< 0.1
ALT (U/L)					
> ULN to 3× ULN	36	33	45	48	23
> 3× ULN to 5× ULN	1	4	5	5	1
> 5× ULN	0.7	1	1.3	1.5	0.3

ULN = Upper Limit of Normal

*For a description of these studies, see [Section 14, Clinical Studies](#).

In the all-exposure population, the elevations in ALT and AST remained consistent with what was seen in the 24 week, controlled clinical trials.

In Study WA25204, of the 1538 patients with moderate to severe RA [see [Clinical Studies \(14.1\)](#)] and treated with tocilizumab, elevations in ALT or AST >3 x ULN occurred in 5.3% and 2.2% patients, respectively. One serious event of drug induced hepatitis with hyperbilirubinemia was reported in association with tocilizumab.

Lipids

Elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were first assessed at 6 weeks following initiation of tocilizumab-IV in the controlled 24 week clinical trials. Increases were observed at this time point and remained stable thereafter. Increases in triglycerides to levels above 500 mg per dL were rarely observed. Changes in other lipid parameters from baseline to week 24 were evaluated and are summarized below:

- Mean LDL increased by 13 mg per dL in the tocilizumab 4 mg per kg+DMARD arm, 20 mg per dL in the tocilizumab 8 mg per kg+DMARD, and 25 mg per dL in tocilizumab 8 mg per kg monotherapy.
- Mean HDL increased by 3 mg per dL in the tocilizumab 4 mg per kg+DMARD arm, 5 mg per dL in the tocilizumab 8 mg per kg+DMARD, and 4 mg per dL in tocilizumab 8 mg per kg monotherapy.
- Mean LDL/HDL ratio increased by an average of 0.14 in the tocilizumab 4 mg per kg+DMARD arm, 0.15 in the tocilizumab 8 mg per kg+DMARD, and 0.26 in tocilizumab 8 mg per kg monotherapy.

- ApoB/ApoA1 ratios were essentially unchanged in tocilizumab-treated patients.

Elevated lipids responded to lipid lowering agents.

In the all-exposure population, the elevations in lipid parameters remained consistent with what was seen in the 24 week, controlled clinical trials.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other tocilizumab products may be misleading.

In the 24 week, controlled clinical studies, a total of 2876 patients have been tested for anti-tocilizumab antibodies. Forty-six patients (2%) developed positive anti-tocilizumab antibodies, of whom 5 had an associated, medically significant, hypersensitivity reaction leading to withdrawal. Thirty patients (1%) developed neutralizing antibodies.

Malignancies

During the 24 week, controlled period of the studies, 15 malignancies were diagnosed in patients receiving tocilizumab-IV, compared to 8 malignancies in patients in the control groups. Exposure-adjusted incidence was similar in the tocilizumab-IV 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 [*see Warnings and Precautions (5.5)*].

Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on 4 or 8 mg per kg tocilizumab-IV plus DMARD and at least 1% greater than that observed in patients on placebo plus DMARD are summarized in [Table 2](#).

Table 2 Adverse Reactions Occurring in at Least 2% or More of Patients on 4 or 8 mg per kg Tocilizumab plus DMARD and at Least 1% Greater Than That Observed in Patients on Placebo plus DMARD

24 Week Phase 3 Controlled Study Population					
Preferred Term	Tocilizumab 8 mg per kg MONOTHERAPY N = 288 (%)	Methotrexate N = 284 (%)	Tocilizumab 4 mg per kg + DMARDs N = 774 (%)	Tocilizumab 8 mg per kg + DMARDs N = 1582 (%)	Placebo + DMARDs N = 1170 (%)
Upper Respiratory Tract Infection	7	5	6	8	6
Nasopharyngitis	7	6	4	6	4
Headache	7	2	6	5	3
Hypertension	6	2	4	4	3
ALT increased	6	4	3	3	1
Dizziness	3	1	2	3	2
Bronchitis	3	2	4	3	3
Rash	2	1	4	3	1
Mouth Ulceration	2	2	1	2	1
Abdominal Pain Upper	2	2	3	3	2
Gastritis	1	2	1	2	1
Transaminase increased	1	5	2	2	1

Other infrequent and medically relevant adverse reactions occurring at an incidence less than 2% in rheumatoid arthritis patients treated with tocilizumab-IV in controlled trials were:

Infections and Infestations: oral herpes simplex

Gastrointestinal disorders: stomatitis, gastric ulcer

Investigations: weight increased, total bilirubin increased

Blood and lymphatic system disorders: leukopenia

General disorders and administration site conditions: edema peripheral

Respiratory, thoracic, and mediastinal disorders: dyspnea, cough

Eye disorders: conjunctivitis

Renal disorders: nephrolithiasis

Endocrine disorders: hypothyroidism

6.2 Clinical Trials Experience in Polyarticular Juvenile Idiopathic Arthritis Patients Treated with Intravenous Tocilizumab (Tocilizumab-IV)

The safety of tocilizumab-IV was studied in 188 pediatric patients 2 to 17 years of age with PJA who had an inadequate clinical response or were intolerant to methotrexate. The total patient exposure in the tocilizumab-IV all exposure population (defined as patients who received at least one dose of tocilizumab-IV) was 184.4 patient years. At baseline, approximately half of the

patients were taking oral corticosteroids and almost 80% were taking methotrexate. In general, the types of adverse drug reactions in patients with PJIA were consistent with those seen in RA and SJIA patients [see *Adverse Reactions (6.1 and 6.3)*].

Infections

The rate of infections in the tocilizumab-IV all exposure population was 163.7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing less than 30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing at or above 30 kg, treated with 8 mg/kg tocilizumab (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing less than 30 kg treated with 10 mg/kg tocilizumab (21%) compared to patients weighing at or above 30 kg, treated with 8 mg/kg tocilizumab (8%).

Infusion Reactions

In PJIA patients, infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion. In the tocilizumab-IV all exposure population, 11 patients (6%) experienced an event during the infusion, and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occurring during infusion were headache, nausea and hypotension, and occurring within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and SJIA patients [see *Adverse Reactions (6.1 and 6.3)*].

No clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported.

Immunogenicity

One patient, in the 10 mg/kg less than 30 kg group, developed positive anti-tocilizumab antibodies without developing a hypersensitivity reaction and subsequently withdrew from the study.

Laboratory Abnormalities

Neutropenia

During routine laboratory monitoring in the tocilizumab-IV all exposure population, a decrease in neutrophil counts below 1×10^9 per L occurred in 3.7% of patients.

There was no clear relationship between decreases in neutrophils below 1×10^9 per L and the occurrence of serious infections.

Thrombocytopenia

During routine laboratory monitoring in the tocilizumab-IV all exposure population, 1% of patients had a decrease in platelet count at or less than 50,000 per mm³ without associated bleeding events.

Elevated Liver Enzymes

During routine laboratory monitoring in the tocilizumab-IV all exposure population, elevation in ALT or AST at or greater than 3 x ULN occurred in 4% and less than 1% of patients, respectively.

Lipids

During routine laboratory monitoring in the tocilizumab-IV all exposure population, elevation in total cholesterol greater than 1.5-2 x ULN occurred in one patient (0.5%) and elevation in LDL greater than 1.5-2 x ULN occurred in one patient (0.5%).

6.3 Clinical Trials Experience in Systemic Juvenile Idiopathic Arthritis Patients Treated with Intravenous Tocilizumab (Tocilizumab-IV)

The data described below reflect exposure to tocilizumab-IV in one randomized, double-blind, placebo-controlled trial of 112 pediatric patients with SJIA 2 to 17 years of age who had an inadequate clinical response to nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids due to toxicity or lack of efficacy. At baseline, approximately half of the patients were taking 0.3 mg/kg/day corticosteroids or more, and almost 70% were taking methotrexate. The trial included a 12 week controlled phase followed by an open-label extension. In the 12 week double-blind, controlled portion of the clinical study 75 patients received treatment with tocilizumab-IV (8 or 12 mg per kg based upon body weight). After 12 weeks or at the time of escape, due to disease worsening, patients were treated with tocilizumab-IV in the open-label extension phase.

The most common adverse events (at least 5%) seen in tocilizumab-IV treated patients in the 12 week controlled portion of the study were: upper respiratory tract infection, headache, nasopharyngitis and diarrhea.

Infections

In the 12 week controlled phase, the rate of all infections in the tocilizumab-IV group was 345 per 100 patient-years and 287 per 100 patient-years in the placebo group. In the open label extension over an average duration of 73 weeks of treatment, the overall rate of infections was 304 per 100 patient-years.

In the 12 week controlled phase, the rate of serious infections in the tocilizumab-IV group was 11.5 per 100 patient years. In the open label extension over an average duration of 73 weeks of treatment, the overall rate of serious infections was 11.4 per 100 patient years. The most commonly reported serious infections included pneumonia, gastroenteritis, varicella, and otitis media.

Macrophage Activation Syndrome

In the 12 week controlled study, no patient in any treatment group experienced macrophage activation syndrome (MAS) while on assigned treatment; 3 per 112 (3%) developed MAS during open-label treatment with tocilizumab-IV. One patient in the placebo group escaped to tocilizumab-IV 12 mg per kg at Week 2 due to severe disease activity, and ultimately developed MAS at Day 70. Two additional patients developed MAS during the long-term extension. All 3 patients had tocilizumab-IV dose interrupted (2 patients) or discontinued (1 patient) for the MAS event, received treatment, and the MAS resolved without sequelae. Based on a limited number of cases, the incidence of MAS does not appear to be elevated in the tocilizumab-IV SJIA clinical development experience; however no definitive conclusions can be made.

Infusion Reactions

Patients were not premedicated, however most patients were on concomitant corticosteroids as part of their background treatment for SJIA. Infusion related reactions were defined as all events occurring during or within 24 hours after an infusion. In the 12 week controlled phase, 4% of tocilizumab-IV and 0% of placebo treated patients experienced events occurring during infusion. One event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

Within 24 hours after infusion, 16% of patients in the tocilizumab-IV treatment group and 5% of patients in the placebo group experienced an event. In the tocilizumab-IV group the events included rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious.

Anaphylaxis

Anaphylaxis was reported in 1 out of 112 patients (less than 1%) treated with tocilizumab-IV during the controlled and open label extension study [see *Warnings and Precautions (5.6)*].

Immunogenicity

All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies: one of these patients experienced serious adverse events of urticaria and angioedema consistent with an anaphylactic reaction which led to withdrawal; the other patient developed macrophage activation syndrome while on escape therapy and was discontinued from the study.

Laboratory Abnormalities

Neutropenia

During routine monitoring in the 12 week controlled phase, a decrease in neutrophil below 1×10^9 per L occurred in 7% of patients in the tocilizumab-IV group, and in no patients in the placebo group. In the open label extension over an average duration of 73 weeks of treatment, a decreased neutrophil count occurred in 17% of the tocilizumab-IV group. There was no clear

relationship between decrease in neutrophils below 1×10^9 per L and the occurrence of serious infections.

Thrombocytopenia

During routine monitoring in the 12 week controlled phase, 1% of patients in the tocilizumab-IV group and 3% in the placebo group had a decrease in platelet count to no more than 100,000 per mm^3 .

In the open label extension over an average duration of 73 weeks of treatment, decreased platelet count occurred in 4% of patients in the tocilizumab-IV group, with no associated bleeding.

Elevated Liver Enzymes

During routine laboratory monitoring in the 12 week controlled phase, elevation in ALT or AST at or above 3x ULN occurred in 5% and 3% of patients, respectively in the tocilizumab group and in 0% of placebo patients.

In the open label extension over an average duration of 73 weeks of treatment, the elevation in ALT or AST at or above 3x ULN occurred in 13% and 5% of tocilizumab-IV treated patients, respectively.

Lipids

During routine laboratory monitoring in the 12 week controlled phase, elevation in total cholesterol greater than 1.5x ULN – 2x ULN occurred in 1.5% of the tocilizumab-IV group and in 0% of placebo patients. Elevation in LDL greater than 1.5x ULN – 2x ULN occurred in 1.9% of patients in the tocilizumab-IV group and 0% of the placebo group.

In the open label extension study over an average duration of 73 weeks of treatment, the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled study data.

6.4 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of tocilizumab products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Fatal anaphylaxis [*see Warnings and Precautions (5.6)*]
- Stevens-Johnson Syndrome
- Pancreatitis
- Drug-induced liver injury, Hepatitis, Hepatic failure, Jaundice [*see Warnings and Precautions (5.3)*]

7 DRUG INTERACTIONS

7.1 Concomitant Drugs for Treatment of Adult Indications

In RA patients, population pharmacokinetic analyses did not detect any effect of methotrexate (MTX), non-steroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance. Concomitant administration of a single intravenous dose of 10 mg/kg tocilizumab with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure. Tocilizumab products have not been studied in combination with biological DMARDs such as TNF antagonists [see *Dosage and Administration (2.2)*].

7.2 Interactions with CYP450 Substrates

Cytochrome P450s in the liver are down-regulated by infection and inflammation stimuli including cytokines such as IL-6. Inhibition of IL-6 signaling in RA patients treated with tocilizumab products may restore CYP450 activities to higher levels than those in the absence of tocilizumab products leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Its effect on CYP2C8 or transporters is unknown. In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of tocilizumab, respectively. The effect of tocilizumab products on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of TOFIDENCE, in patients being treated with these types of medicinal products, perform therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) and the individual dose of the medicinal product adjusted as needed. Exercise caution when coadministering TOFIDENCE with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of tocilizumab products on CYP450 enzyme activity may persist for several weeks after stopping therapy [see *Clinical Pharmacology (12.3)*].

7.3 Live Vaccines

Avoid use of live vaccines concurrently with TOFIDENCE [see *Warnings and Precautions (5.9)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data with tocilizumab products in pregnant women are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage. Monoclonal antibodies, such as tocilizumab products, are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the *in utero* exposed infant [see *Clinical Considerations*]. In animal reproduction studies, intravenous administration of tocilizumab to Cynomolgus monkeys during organogenesis caused abortion/embryo-fetal death at doses 1.25 times and higher than the maximum recommended human dose by the intravenous route of 8 mg per kg every 2 to 4 weeks. The literature in animals suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition [see *Data*]. Based on the animal data, there may be a potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to TOFIDENCE *in utero* [see *Warnings and Precautions (5.9)*].

Data

Animal Data

An embryo-fetal developmental toxicity study was performed in which pregnant Cynomolgus monkeys were treated intravenously with tocilizumab at daily doses of 2, 10, or 50 mg/kg during organogenesis from gestation day (GD) 20-50. Although there was no evidence for a teratogenic/dysmorphogenic effect at any dose, tocilizumab produced an increase in the incidence of abortion/embryo-fetal death at doses 1.25 times and higher the MRHD by the intravenous route at maternal intravenous doses of 10 and 50 mg/kg. Testing of a murine analogue of tocilizumab in mice did not yield any evidence of harm to offspring during the pre- and postnatal development phase when dosed at 50 mg/kg intravenously with treatment every three days from implantation (GD 6) until post-partum day 21 (weaning). There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring.

Parturition is associated with significant increases of IL-6 in the cervix and myometrium. The literature suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition. For mice deficient in IL-6 (Il6^{-/-} null mice), parturition was delayed relative to wild-type (Il6^{+/+}) mice. Administration of recombinant IL-6 to Il6^{-/-} null mice restored the normal timing of delivery.

8.2 Lactation

Risk Summary

No information is available on the presence of tocilizumab products in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Maternal immunoglobulin G (IgG) is present in human milk. If tocilizumab products are transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to tocilizumab products are unknown.

The lack of clinical data during lactation precludes clear determination of the risk of tocilizumab products to an infant during lactation; therefore the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TOFIDENCE and the potential adverse effects on the breastfed child from Tofidence or from the underlying maternal condition.

8.4 Pediatric Use

TOFIDENCE by intravenous use is indicated for the treatment of pediatric patients with:

- Active systemic juvenile idiopathic arthritis in patients 2 years of age and older
- Active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older

The safety and effectiveness of TOFIDENCE in pediatric patients with conditions other than PJIA or SJIA have not been established. The safety and effectiveness in pediatric patients below the age of 2 have not been established in PJIA or SJIA.

Systemic Juvenile Idiopathic Arthritis – Intravenous Use

A multicenter, open-label, single arm study to evaluate the PK, safety and exploratory PD and efficacy of tocilizumab over 12-weeks in SJIA patients (N=11) under 2 years of age was conducted. Patients received intravenous tocilizumab 12 mg/kg every two weeks. Concurrent use of stable background treatment with corticosteroids, MTX, and/or non-steroidal anti-inflammatory drugs was permitted. Patients who completed the 12-week period could continue to the optional extension period (a total of 52-weeks or until the age of 2 years, whichever was longer).

The primary PK endpoints (C_{max}, C_{trough} and AUC_{2weeks}) of tocilizumab at steady-state in this study were within the ranges of these parameters observed in patients with SJIA aged 2 to 17 years.

The safety and immunogenicity of tocilizumab for patients with SJIA under 2 years of age was assessed descriptively. SAEs, AEs leading to discontinuation, and infectious AEs were reported by 27.3%, 36.4%, and 81.8% of patients. Six patients (54.5%) experienced hypersensitivity reactions, defined as all adverse events occurring during or within 24 hours after an infusion considered related to tocilizumab. Three of these patients experienced serious hypersensitivity reactions and were withdrawn from the study. Three patients with hypersensitivity reactions (two with serious hypersensitivity reactions) developed treatment induced anti-tocilizumab antibodies after the event. There were no cases of MAS based on the protocol-specified criteria, but 2 cases of suspected MAS based on Ravelli criteria¹.

8.5 Geriatric Use

Of the 2644 patients who received tocilizumab in Studies I to V [see *Clinical Studies (14)*], a total of 435 rheumatoid arthritis patients were 65 years of age and older, including 50 patients 75 years and older. The frequency of serious infection among tocilizumab treated subjects 65 years of age and older was higher than those under the age of 65. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

8.6 Hepatic Impairment

The safety and efficacy of tocilizumab products have not been studied in patients with hepatic impairment, including patients with positive HBV and HCV serology [see *Warnings and Precautions (5.8)*].

8.7 Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Tocilizumab products have not been studied in patients with severe renal impairment [see *Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

No studies on the potential for tocilizumab products to cause dependence have been performed. However, there is no evidence from the available data that tocilizumab products treatment results in dependence.

¹ Ravelli A, Minoia F, Davi S on behalf of the Paediatric Rheumatology International Trials Organisation, the Childhood Arthritis and Rheumatology Research Alliance, the Pediatric Rheumatology Collaborative Study Group, and the Histiocyte Society, *et al.* 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis. *Annals of the Rheumatic Diseases* 2016;75:481-489.

10 OVERDOSAGE

There are limited data available on overdoses with tocilizumab products. One case of accidental overdose was reported with intravenous tocilizumab in which a patient with multiple myeloma received a dose of 40 mg per kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received single doses of up to 28 mg per kg, although all 5 patients at the highest dose of 28 mg per kg developed dose-limiting neutropenia.

In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate symptomatic treatment.

11 DESCRIPTION

Tocilizumab-bavi is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1 κ (gamma 1, kappa) subclass with a typical H₂L₂ polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. Tocilizumab-bavi has a molecular weight of approximately 148 kDa. The antibody is produced in mammalian (Chinese hamster ovary) cells.

Intravenous Infusion

TOFIDENCE (tocilizumab-bavi) injection is a sterile, clear to opalescent, colorless to light yellow, preservative-free solution for further dilution prior to intravenous infusion with a pH of approximately 6.2. Each single-dose vial, formulated in an aqueous solution, is available at a concentration of 20 mg/mL containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of TOFIDENCE. Each mL of solution contains arginine hydrochloride (10.53 mg), histidine (0.81 mg), L-histidine hydrochloride monohydrate (1.01 mg), polysorbate 80 (0.5 mg), sucrose (20 mg), and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tocilizumab products bind to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. 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.

12.2 Pharmacodynamics

In clinical studies in RA patients with the 4 mg per kg and 8 mg per kg intravenous doses decreases in levels of C-reactive protein (CRP) to within normal ranges were seen as early as week 2. Changes in pharmacodynamic parameters were observed (i.e., decreases in rheumatoid factor, erythrocyte sedimentation rate (ESR), serum amyloid A, fibrinogen and increases in hemoglobin) with doses, however the greatest improvements were observed with 8 mg per kg tocilizumab. Pharmacodynamic changes were also observed to occur after tocilizumab administration in PJIA and SJIA patients (decreases in CRP, ESR, and increases in hemoglobin). The relationship between these pharmacodynamic findings and clinical efficacy is not known.

In healthy subjects administered tocilizumab in doses from 2 to 28 mg per kg intravenously, absolute neutrophil counts decreased to the nadir 3 to 5 days following tocilizumab administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Rheumatoid arthritis patients demonstrated a similar pattern of absolute neutrophil counts following tocilizumab administration [see *Warnings and Precautions (5.4)*].

12.3 Pharmacokinetics

PK 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. Population pharmacokinetic analyses in any patient population tested so far indicate no relationship between apparent clearance and the presence of anti-drug antibodies.

Rheumatoid Arthritis - Intravenous Administration

The pharmacokinetics in healthy subjects and RA patients suggest that PK is similar between the two populations.

The population PK model was developed from an analysis dataset composed of an IV dataset of 1793 patients from Study I, Study III, Study IV, and Study V. C_{mean} is included in place of AUC_{tau} , since for dosing regimens with different inter-dose intervals, the mean concentration over the dosing period characterizes the comparative exposure better than AUC_{tau} .

At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, a terminal half-life of approximately 21.5 days was derived from the population parameter estimates.

For doses of 4 mg/kg tocilizumab given every 4 weeks intravenously, the estimated median (range) C_{max} , C_{trough} , and C_{mean} of tocilizumab at steady state were 86.1 (44.8–202) mcg/mL, 0.1

(0.0–14.6) mcg/mL, and 18.0 (8.9–50.7) mcg/mL, respectively. For doses of 8 mg/kg tocilizumab given every 4 weeks intravenously, the estimated median (range) C_{max} , C_{trough} , and C_{mean} of tocilizumab were 176 (75.4–557) mcg/mL, 13.4 (0.1–154) mcg/mL, and 54.0 (17–260) mcg/mL, respectively. C_{max} increased dose-proportionally between doses of 4 and 8 mg/kg IV every 4 weeks, while a greater than dose-proportional increase was observed in C_{mean} and C_{trough} . At steady-state, C_{mean} and C_{trough} were 3.0 and 134 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

The accumulation ratios for AUC and C_{max} after multiple doses of 4 and 8 mg/kg IV Q4W are low, while the accumulation ratios for C_{trough} are higher (2.62 and 2.47, respectively). For C_{max} , greater than 90% of the steady-state value was reached after the 1st IV infusion. For AUC_{tau} and C_{mean} , 90% of the steady-state value was reached after the 1st and 3rd infusion for 4 mg/kg and 8 mg/kg IV, while for C_{trough} , approximately 90% of the steady-state value was reached after the 4th IV infusion after both doses.

Population PK analysis identified body weight as a significant covariate impacting the pharmacokinetics of tocilizumab. When given IV on a mg/kg basis, individuals with body weight ≥ 100 kg are predicted to have mean steady-state exposures higher than mean values for the patient population. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients with RA [see *Dosage and Administration (2.1)*].

Polyarticular Juvenile Idiopathic Arthritis – Intravenous Administration

The pharmacokinetics of tocilizumab (TCZ) in PJIA patients was characterized by a population pharmacokinetic analysis which included 188 patients who were treated with TCZ IV.

For doses of 8 mg/kg tocilizumab (patients with a body weight at or above 30 kg) given every 4 weeks intravenously, the estimated median (range) C_{max} , C_{trough} , and C_{mean} of tocilizumab at steady state were 181 (114–331) mcg/mL, 3.28 (0.02–35.4) mcg/mL, and 38.6 (22.2–83.8) mcg/mL, respectively. For doses of 10 mg/kg tocilizumab (patients with a body weight less than 30 kg) given every 4 weeks intravenously, the estimated median (range) C_{max} , C_{trough} , and C_{mean} of tocilizumab were 167 (125–220) mcg/mL, 0.35 (0–11.8) mcg/mL, and 30.8 (16.0–48.0) mcg/mL, respectively.

The accumulation ratios were 1.05 and 1.16 for AUC_{4weeks}, and 1.43 and 2.22 for C_{trough} for 10 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) intravenous doses, respectively. No accumulation for C_{max} was observed. Following 10 mg/kg and 8 mg/kg TCZ IV every 4 weeks doses in PJIA patients (aged 2 to 17 years), steady state concentrations (trough and average) were within the range of exposures in adult RA patients following 4 mg/kg and 8 mg/kg every 4 weeks, and steady state peak concentrations in PJIA patients were comparable to those following 8 mg/kg every 4 weeks in adult RA patients.

Systemic Juvenile Idiopathic Arthritis—Intravenous Administration

The pharmacokinetics of tocilizumab (TCZ) in SJIA patients was characterized by a population pharmacokinetic analysis which included 89 patients who were treated with TCZ IV.

For doses of 8 mg/kg tocilizumab (patients with a body weight at or above 30 kg) given every 2 weeks intravenously, the estimated median (range) C_{\max} , C_{trough} , and C_{mean} of tocilizumab were 253 (120–404) mcg/mL, 70.7 (5.26–127) mcg/mL, and 117 (37.6–199) mcg/mL, respectively. For doses of 12 mg/kg tocilizumab (patients with a body weight less than 30 kg) given every 2 weeks intravenously, the estimated median (range) C_{\max} , C_{trough} , and C_{mean} of tocilizumab were 274 (149–444) mcg/mL, 65.9 (19.0–135) mcg/mL, and 124 (60–194) mcg/mL, respectively.

The accumulation ratios were 1.95 and 2.01 for $AUC_{4\text{weeks}}$, and 3.41 and 3.20 for C_{trough} for 12 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) intravenous doses, respectively. Accumulation data for C_{\max} were 1.37 and 1.42 for 12 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) intravenous doses, respectively. Following every other week dosing with tocilizumab IV, steady state was reached by 8 weeks for both body weight groups. Mean estimated tocilizumab exposure parameters were similar between the two dose groups defined by body weight.

Distribution

Following intravenous dosing, tocilizumab undergoes biphasic elimination from the circulation. In rheumatoid arthritis patients the central volume of distribution was 3.5 L and the peripheral volume of distribution was 2.9 L, resulting in a volume of distribution at steady state of 6.4 L.

In pediatric patients with PJIA, the central volume of distribution was 1.98 L, the peripheral volume of distribution was 2.1 L, resulting in a volume of distribution at steady state of 4.08 L.

In pediatric patients with SJIA, the central volume of distribution was 1.87 L, the peripheral volume of distribution was 2.14 L resulting in a volume of distribution at steady state of 4.01 L.

Elimination

Tocilizumab is eliminated by a combination of linear clearance and nonlinear elimination. The concentration-dependent nonlinear elimination plays a major role at low tocilizumab concentrations. Once the nonlinear pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance. The saturation of the nonlinear elimination leads to an increase in exposure that is more than dose-proportional. The pharmacokinetic parameters of tocilizumab do not change with time.

Population pharmacokinetic analyses in any patient population tested so far indicate no relationship between apparent clearance and the presence of anti-drug antibodies.

The linear clearance in the population pharmacokinetic analysis was estimated to be 12.5 mL per h in RA patients, 5.8 mL per h in pediatric patients with PJIA, and 5.7 mL per h in pediatric patients with SJIA.

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.

For intravenous administration in RA patients, the concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg per kg and up to 13 days for 8 mg per kg every 4 weeks in patients with RA at steady-state.

The $t_{1/2}$ of tocilizumab in children with PJIA is up to 17 days for the two body weight categories (8 mg/kg for body weight at or above 30 kg or 10 mg/kg for body weight below 30 kg) during a dosing interval at steady state.

The $t_{1/2}$ of tocilizumab intravenous in pediatric patients with SJIA is up to 16 days for the two body weight categories (8 mg/kg for body weight at or above 30 kg and 12 mg/kg for body weight below 30 kg every other week) during a dosing interval at steady-state.

Specific Populations

Population pharmacokinetic analyses in adult rheumatoid arthritis patients showed that age, gender and race did not affect the pharmacokinetics of tocilizumab. Linear clearance was found to increase with body size. In RA patients, the body weight-based dose (8 mg per kg) resulted in approximately 86% higher exposure in patients who are greater than 100 kg in comparison to patients who are less than 60 kg.

Patients with Hepatic Impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab was conducted.

Patients with Renal Impairment

No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab was conducted.

Most of the RA patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance less than 80 mL per min and at or above 50 mL per min based on Cockcroft-Gault formula) did not impact the pharmacokinetics of tocilizumab.

No dose adjustment is required in patients with mild or moderate renal impairment.

Drug Interaction Studies

In vitro data suggested that IL-6 reduced mRNA expression for several CYP450 isoenzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and this reduced expression was reversed by co-incubation with tocilizumab at clinically relevant concentrations. Accordingly, inhibition of IL-6 signaling in RA patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased

metabolism of drugs that are CYP450 substrates. Its effect on CYP2C8 or transporters (e.g., P-gp) is unknown. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation of TOFIDENCE, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Caution should be exercised when TOFIDENCE is coadministered with drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives (CYP3A4 substrates) [see *Drug Interactions (7.2)*].

Simvastatin

Simvastatin is a CYP3A4 and OATP1B1 substrate. In 12 RA patients not treated with tocilizumab, receiving 40 mg simvastatin, exposures of simvastatin and its metabolite, simvastatin acid, was 4- to 10-fold and 2-fold higher, respectively, than the exposures observed in healthy subjects. One week following administration of a single infusion of tocilizumab (10 mg per kg), exposure of simvastatin and simvastatin acid decreased by 57% and 39%, respectively, to exposures that were similar or slightly higher than those observed in healthy subjects. Exposures of simvastatin and simvastatin acid increased upon withdrawal of tocilizumab in RA patients. Selection of a particular dose of simvastatin in RA patients should take into account the potentially lower exposures that may result after initiation of TOFIDENCE, (due to normalization of CYP3A4) or higher exposures after discontinuation of TOFIDENCE.

Omeprazole

Omeprazole is a CYP2C19 and CYP3A4 substrate. In RA patients receiving 10 mg omeprazole, exposure to omeprazole was approximately 2 fold higher than that observed in healthy subjects. In RA patients receiving 10 mg omeprazole, before and one week after tocilizumab infusion (8 mg per kg), the omeprazole AUC_{inf} decreased by 12% for poor (N=5) and intermediate metabolizers (N=5) and by 28% for extensive metabolizers (N=8) and were slightly higher than those observed in healthy subjects.

Dextromethorphan

Dextromethorphan is a CYP2D6 and CYP3A4 substrate. In 13 RA patients receiving 30 mg dextromethorphan, exposure to dextromethorphan was comparable to that in healthy subjects. However, exposure to its metabolite, dextrorphan (a CYP3A4 substrate), was a fraction of that observed in healthy subjects. One week following administration of a single infusion of tocilizumab (8 mg per kg), dextromethorphan exposure was decreased by approximately 5%. However, a larger decrease (29%) in dextrorphan levels was noted after tocilizumab infusion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to establish the carcinogenicity potential of tocilizumab products. Literature indicates that the IL-6 pathway can mediate anti-tumor responses by promoting increased immune cell surveillance of the tumor microenvironment. However, available published evidence also supports that IL-6 signaling through the IL-6

receptor may be involved in pathways that lead to tumorigenesis. The malignancy risk in humans from an antibody that disrupts signaling through the IL-6 receptor, such as tocilizumab, is presently unknown.

Fertility and reproductive performance were unaffected in male and female mice that received a murine analogue of tocilizumab administered by the intravenous route at a dose of 50 mg/kg every three days.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis—Intravenous Administration

The efficacy and safety of intravenously administered tocilizumab was assessed in five randomized, double-blind, multicenter studies in patients greater than 18 years with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 8 tender and 6 swollen joints at baseline. Tocilizumab was given intravenously every 4 weeks as monotherapy (Study I), in combination with methotrexate (MTX) (Studies II and III) or other disease-modifying anti-rheumatic drugs (DMARDs) (Study IV) in patients with an inadequate response to those drugs, or in combination with MTX in patients with an inadequate response to TNF antagonists (Study V).

Study I (NCT00109408) evaluated patients with moderate to severe active rheumatoid arthritis who had not been treated with MTX within 24 weeks prior to randomization, or who had not discontinued previous methotrexate treatment as a result of clinically important toxic effects or lack of response. In this study, 67% of patients were MTX-naïve, and over 40% of patients had rheumatoid arthritis less than 2 years. Patients received tocilizumab 8 mg per kg monotherapy or MTX alone (dose titrated over 8 weeks from 7.5 mg to a maximum of 20 mg weekly). The primary endpoint was the proportion of tocilizumab patients who achieved an ACR 20 response at Week 24.

Study II (NCT00106535) was a 104-week study with an optional 156-week extension phase that evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to MTX. Patients received tocilizumab 8 mg per kg, tocilizumab 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). Upon completion of 52-weeks, patients received open-label treatment with tocilizumab 8 mg per kg through 104 weeks or they had the option to continue their double-blind treatment if they maintained a greater than 70% improvement in swollen/tender joint count. Two pre-specified interim analyses at week 24 and week 52 were conducted. The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response. At weeks 52 and 104, the primary endpoints were change from baseline in modified total Sharp-Genant score and the area under the curve (AUC) of the change from baseline in HAQ-DI score.

Study III (NCT00106548) evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to MTX. Patients received tocilizumab 8 mg per kg, tocilizumab 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg

weekly). The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Study IV (NCT00106574) evaluated patients who had an inadequate response to their existing therapy, including one or more DMARDs. Patients received tocilizumab 8 mg per kg or placebo every four weeks, in combination with the stable DMARDs. The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Study V (NCT00106522) evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy was discontinued prior to randomization. Patients received tocilizumab 8 mg per kg, tocilizumab 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Clinical Response

The percentages of intravenous tocilizumab-treated patients achieving ACR 20, 50 and 70 responses are shown in [Table 3](#). In all intravenous studies, patients treated with 8 mg per kg tocilizumab had higher ACR 20, ACR 50, and ACR 70 response rates versus MTX- or placebo-treated patients at week 24.

During the 24 week controlled portions of Studies I to V, patients treated with tocilizumab at a dose of 4 mg per kg in patients with inadequate response to DMARDs or TNF antagonist therapy had lower response rates compared to patients treated with tocilizumab 8 mg per kg.

Table 3 Clinical Response at Weeks 24 and 52 in Active and Placebo Controlled Trials of Intravenous Tocilizumab (Percent of Patients)

Response Rate	Percent of Patients												
	Study I		Study II			Study III			Study IV		Study V		
	MTX	Tocilizumab 8 mg per kg	Placebo + MTX	Tocilizumab 4 mg per kg + MTX	Tocilizumab 8 mg per kg + MTX	Placebo + MTX	Tocilizumab 4 mg per kg + MTX	Tocilizumab 8 mg per kg + MTX	Placebo + DMARDs	Tocilizumab 8 mg per kg + DMARDs	Placebo + MTX	Tocilizumab 4 mg per kg + MTX	Tocilizumab 8 mg per kg + MTX
	N=284	N=286	N=393	N=399	N=398	N=204	N=213	N=205	N=413	N=803	N=158	N=161	N=170
		(95% CI) ^a		(95% CI) ^a	(95% CI) ^a		(95% CI) ^a	(95% CI) ^a		(95% CI) ^a	(95% CI) ^a	(95% CI) ^a	(95% CI) ^a
ACR 20													
Week 24	53%	70% (0.11, 0.27)	27%	51% (0.17, 0.29)	56% (0.23, 0.35)	27%	48% (0.15, 0.32)	59% (0.23, 0.41)	24%	61% (0.30, 0.40)	10%	30% (0.15, 0.36)	50% (0.36, 0.56)
Week 52	N/A	N/A	25%	47% (0.15, 0.28)	56% (0.25, 0.38)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ACR 50													
Week 24	34%	44% (0.04, 0.20)	10%	25% (0.09, 0.20)	32% (0.16, 0.28)	11%	32% (0.13, 0.29)	44% (0.25, 0.41)	9%	38% (0.23, 0.33)	4%	17% (0.05, 0.25)	29% (0.21, 0.41)
Week 52	N/A	N/A	10%	29% (0.14, 0.25)	36% (0.21, 0.32)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ACR 70													
Week 24	15%	28% (0.07, 0.22)	2%	11% (0.03, 0.13)	13% (0.05, 0.15)	2%	12% (0.04, 0.18)	22% (0.12, 0.27)	3%	21% (0.13, 0.21)	1%	5% (-0.06, 0.14)	12% (0.03, 0.22)
Week 52	N/A	N/A	4%	16% (0.08, 0.17)	20% (0.12, 0.21)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Major Clinical Responses^b													
Week 52	N/A	N/A	1%	4% (0.01, 0.06)	7% (0.03, 0.09)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

^a CI: 95% confidence interval of the weighted difference to placebo adjusted for site (and disease duration for Study I only)

^b Major clinical response is defined as achieving an ACR 70 response for a continuous 24 week period

In study II, a greater proportion of patients treated with 4 mg per kg and 8 mg per kg tocilizumab + MTX achieved a low level of disease activity as measured by a DAS 28-ESR less than 2.6 compared with placebo +MTX treated patients at week 52. The proportion of tocilizumab-treated patients achieving DAS 28-ESR less than 2.6, and the number of residual active joints in these responders in Study II are shown in [Table 4](#).

Table 4 Proportion of Patients with DAS28-ESR Less Than 2.6 with Number of Residual Active Joints in Trials of Intravenous Tocilizumab

Study II			
	Placebo + MTX	Tocilizumab 4 mg per kg + MTX	Tocilizumab 8 mg per kg + MTX
	N = 393	N = 399	N = 398
DAS28-ESR less than 2.6			
Proportion of responders at week 52 (n) 95% confidence interval	3% (12)	18% (70) 0.10, 0.19	32% (127) 0.24, 0.34
Of responders, proportion with 0 active joints (n)	33% (4)	27% (19)	21% (27)
Of responders, proportion with 1 active joint (n)	8% (1)	19% (13)	13% (16)
Of responders, proportion with 2 active joints (n)	25% (3)	13% (9)	20% (25)
Of responders, proportion with 3 or more active joints (n)	33% (4)	41% (29)	47% (59)

*n denotes numerator of all the percentage. Denominator is the intent-to-treat population. Not all patients received DAS28 assessments at Week 52.

The results of the components of the ACR response criteria for Studies III and V are shown in [Table 5](#). Similar results to Study III were observed in Studies I, II and IV.

Table 5 Components of ACR Response at Week 24 in Trials of Intravenous Tocilizumab

Component (mean)	Study III						Study V					
	Tocilizumab 4 mg per kg + MTX		Tocilizumab 8 mg per kg + MTX		Placebo + MTX		Tocilizumab 4 mg per kg + MTX		Tocilizumab 8 mg per kg + MTX		Placebo + MTX	
	N=213		N=205		N=204		N=161		N=170		N=158	
	Baseline	Week 24 ^a	Baseline	Week 24 ^a	Baseline	Week 24	Baseline	Week 24 ^a	Baseline	Week 24 ^a	Baseline	Week 24
Number of tender joints (0-68)	33	19 -7.0 (-10.0, -4.1)	32	14.5 -9.6 (-12.6, -6.7)	33	25	31	21 -10.8 (-14.6, -7.1)	32	17 -15.1 (-18.8, -11.4)	30	30
Number of swollen joints (0-66)	20	10 -4.2 (-6.1, -2.3)	19.5	8 -6.2 (-8.1, -4.2)	21	15	19.5	13 -6.2 (-9.0, -3.5)	19	11 -7.2 (-9.9, -4.5)	19	18
Pain ^b	61	33 -11.0 (-17.0, -5.0)	60	30 -15.8 (-21.7, -9.9)	57	43	63.5	43 -12.4 (-22.1, -2.1)	65	33 -23.9 (-33.7, -14.1)	64	48
Patient global assessment ^b	66	34 -10.9 (-17.1, -4.8)	65	31 -14.9 (-20.9, -8.9)	64	45	70	46 -10.0 (-20.3, 0.3)	70	36 -17.4 (-27.8, -7.0)	71	51
Physician global assessment ^b	64	26 -5.6 (-10.5, -0.8)	64	23 -9.0 (-13.8, -4.2)	64	32	66.5	39 -10.5 (-18.6, -2.5)	66	28 -18.2 (-26.3, -10.0)	67.5	43
Disability index (HAQ) ^c	1.64	1.01 -0.18 (-0.34, -0.02)	1.55	0.96 -0.21 (-0.37, -0.05)	1.55	1.21	1.67	1.39 -0.25 (-0.42, -0.09)	1.75	1.34 -0.34 (-0.51, -0.17)	1.70	1.58
CRP (mg per dL)	2.79	1.17 -1.30 (-2.0, -0.59)	2.61	0.25 -2.156 (-2.86, -1.46)	2.36	1.89	3.11	1.77 -1.34 (-2.5, -0.15)	2.80	0.28 -2.52 (-3.72, -1.32)	3.705	3.06

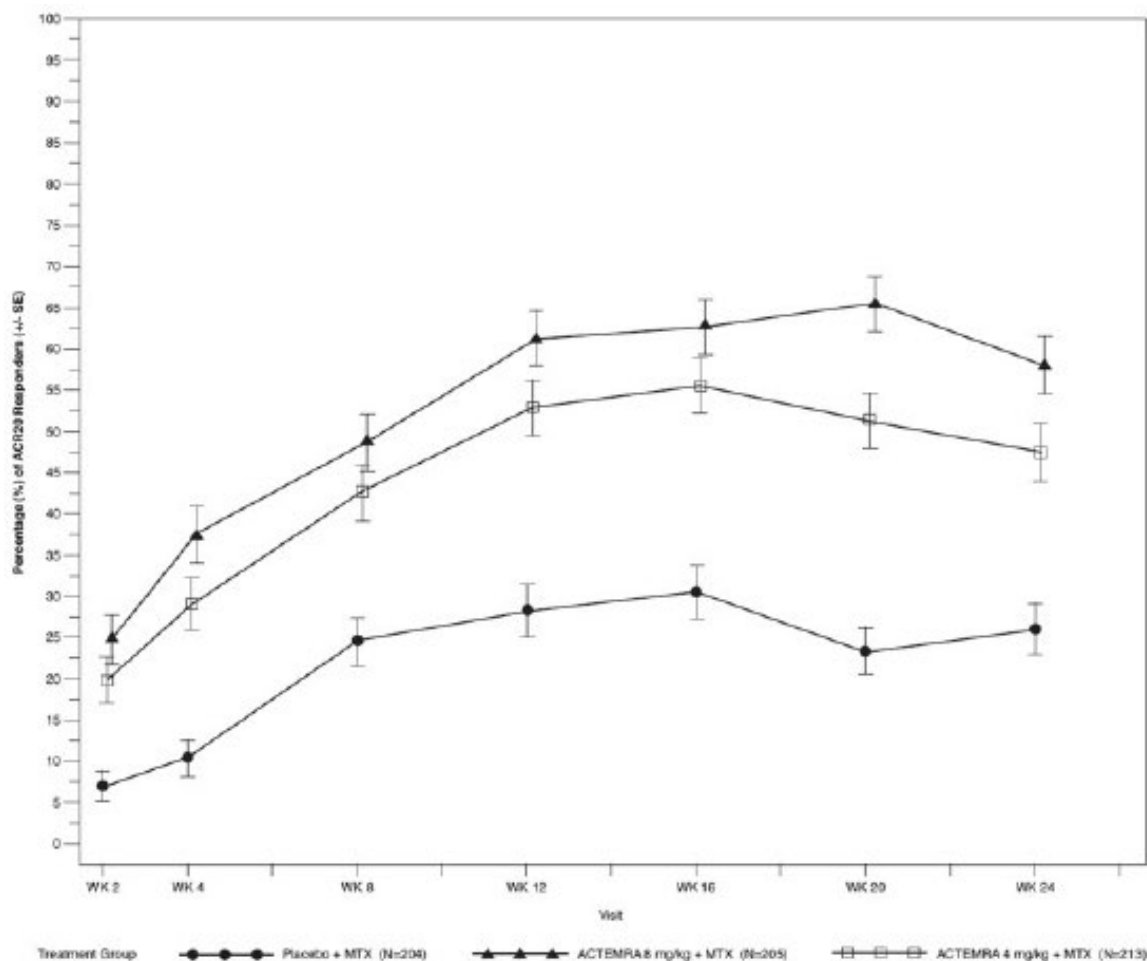
^a Data shown is mean at week 24, difference in adjusted mean change from baseline compared with placebo + MTX at week 24 and 95% confidence interval for that difference

^b Visual analog scale: 0 = best, 100 = worst

^c Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities

The percent of ACR 20 responders by visit for Study III is shown in Figure 1. Similar response curves were observed in studies I, II, IV, and V.

Figure 1 Percent of ACR 20 Responders by Visit for Study III (Inadequate Response to MTX)*



*The same patients may not have responded at each timepoint.

Radiographic Response

In Study II, structural joint damage was assessed radiographically and expressed as change in total Sharp-Genant score and its components, the erosion score and joint space narrowing score. Radiographs of hands/wrists and forefeet were obtained at baseline, 24 weeks, 52 weeks, and 104 weeks and scored by readers unaware of treatments group and visit number. The results from baseline to week 52 are shown in Table 6. tocilizumab 4 mg per kg slowed (less than 75% inhibition compared to the control group) and tocilizumab 8 mg per kg inhibited (at least 75% inhibition compared to the control group) the progression of structural damage compared to placebo plus MTX at week 52.

Table 6 Mean Radiographic Change from Baseline to Week 52 in Study II

	Placebo + MTX	Tocilizumab 4 mg per kg + MTX	Tocilizumab 8 mg per kg + MTX
	N=294	N=343	N=353
Week 52*			
Total Sharp-Genant Score, Mean (SD)	1.17 (3.14)	0.33 (1.30)	0.25 (0.98)
Adjusted Mean difference** (95%CI)		-0.83 (-1.13, -0.52)	-0.90 (-1.20, -0.59)
Erosion Score, Mean (SD)	0.76 (2.14)	0.20 (0.83)	0.15 (0.77)
Adjusted Mean difference** (95%CI)		-0.55 (-0.76, -0.34)	-0.60 (-0.80, -0.39)
Joint Space Narrowing Score, Mean (SD)	0.41 (1.71)	0.13 (0.72)	0.10 (0.49)
Adjusted Mean difference** (95%CI)		-0.28 (-0.44, -0.11)	-0.30 (-0.46, -0.14)

* Week 52 analysis employs linearly extrapolated data for patients after escape, withdrawal, or loss to follow up.

** Difference between the adjusted means (tocilizumab + MTX - Placebo + MTX)

SD = standard deviation

The mean change from baseline to week 104 in Total Sharp-Genant Score for the tocilizumab 4 mg per kg groups was 0.47 (SD = 1.47) and for the 8 mg per kg groups was 0.34 (SD = 1.24). By the week 104, most patients in the control (placebo + MTX) group had crossed over to active treatment, and results are therefore not included for comparison. Patients in the active groups may have crossed over to the alternate active dose group, and results are reported per original randomized dose group.

In the placebo group, 66% of patients experienced no radiographic progression (Total Sharp-Genant Score change ≤ 0) at week 52 compared to 78% and 83% in the tocilizumab 4 mg per kg and 8 mg per kg, respectively. Following 104 weeks of treatment, 75% and 83% of patients initially randomized to tocilizumab 4 mg per kg and 8 mg per kg, respectively, experienced no progression of structural damage compared to 66% of placebo treated patients.

Health Related Outcomes

In Study II, physical function and disability were assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI). Both dosing groups of tocilizumab demonstrated a greater improvement compared to the placebo group in the AUC of change from baseline in the HAQ-DI through week 52. The mean change from baseline to week 52 in HAQ-DI was 0.6, 0.5, and 0.4 for tocilizumab 8 mg per kg, tocilizumab 4 mg per kg, and placebo treatment groups, respectively. Sixty-three percent (63%) and sixty percent (60%) of patients in the tocilizumab 8

mg per kg and tocilizumab 4 mg per kg treatment groups, respectively, achieved a clinically relevant improvement in HAQ-DI (change from baseline of ≥ 0.3 units) at week 52 compared to 53% in the placebo treatment group.

Other Health-Related Outcomes

General health status was assessed by the Short Form Health Survey (SF-36) in Studies I – V. Patients receiving tocilizumab demonstrated greater improvement from baseline compared to placebo in the Physical Component Summary (PCS), Mental Component Summary (MCS), and in all 8 domains of the SF-36.

Cardiovascular Outcomes

Study WA25204 (NCT01331837) was a randomized, open-label (sponsor-blinded), 2-arm parallel-group, multi-center, non-inferiority, cardiovascular (CV) outcomes trial in patients with a diagnosis of moderate to severe RA. This CV safety study was designed to exclude a moderate increase in CV risk in patients treated with tocilizumab compared with a TNF inhibitor standard of care (etanercept).

The study included 3,080 seropositive RA patients with active disease and an inadequate response to non-biologic disease-modifying anti-rheumatic drugs, who were aged ≥ 50 years with at least one additional CV risk factor beyond RA. Patients were randomized 1:1 to IV tocilizumab 8 mg/kg Q4W or SC etanercept 50 mg QW and followed for an average of 3.2 years. The primary endpoint was the comparison of the time-to-first occurrence of any component of a composite of major adverse CV events (MACE; non-fatal myocardial infarction, non-fatal stroke, or CV death), with the final intent-to-treat analysis based on a total of 161 confirmed CV events (83/1538 [5.4%] for tocilizumab; 78/1542 [5.1%] for etanercept) reviewed by an independent and blinded adjudication committee.

Non-inferiority of tocilizumab to etanercept for cardiovascular risk was determined by excluding $>80\%$ relative increase in the risk of MACE. The estimated hazard ratio (HR) for the risk of MACE comparing tocilizumab to etanercept was 1.05; 95% CI (0.77, 1.43).

14.2 Polyarticular Juvenile Idiopathic Arthritis—Intravenous Administration

The efficacy of tocilizumab was assessed in a three-part study, WA19977 (NCT00988221), including an open-label extension in children 2 to 17 years of age with active polyarticular juvenile idiopathic arthritis (PJIA), who had an inadequate response to methotrexate or inability to tolerate methotrexate. Patients had at least 6 months of active disease (mean disease duration of 4.2 ± 3.7 years), with at least five joints with active arthritis (swollen or limitation of movement accompanied by pain and/or tenderness) and/or at least 3 active joints having limitation of motion (mean, 20 ± 14 active joints). The patients treated had subtypes of JIA that at disease onset included Rheumatoid Factor Positive or Negative Polyarticular JIA, or Extended Oligoarticular JIA. Treatment with a stable dose of methotrexate was permitted but was not required during the study. Concurrent use of disease modifying antirheumatic drugs (DMARDs),

other than methotrexate, or other biologics (e.g., TNF antagonists or T cell costimulation modulator) were not permitted in the study.

Part I consisted of a 16-week active tocilizumab treatment lead-in period (n=188) followed by Part II, a 24-week randomized double-blind placebo-controlled withdrawal period, followed by Part III, a 64-week open-label period. Eligible patients weighing at or above 30 kg received tocilizumab at 8 mg/kg intravenously once every four weeks. Patients weighing less than 30 kg were randomized 1:1 to receive either tocilizumab 8 mg/kg or 10 mg/kg intravenously every four weeks. At the conclusion of the open-label Part I, 91% of patients taking background MTX in addition to tocilizumab and 83% of patients on tocilizumab monotherapy achieved an ACR 30 response at week 16 compared to baseline and entered the blinded withdrawal period (Part II) of the study. The proportions of patients with JIA ACR 50/70 responses in Part I were 84.0%, and 64%, respectively for patients taking background MTX in addition to tocilizumab and 80% and 55% respectively for patients on tocilizumab monotherapy.

In Part II, patients (ITT, n=163) were randomized to tocilizumab (same dose received in Part I) or placebo in a 1:1 ratio that was stratified by concurrent methotrexate use and concurrent corticosteroid use. Each patient continued in Part II of the study until Week 40 or until the patient satisfied JIA ACR 30 flare criteria (relative to Week 16) and qualified for escape.

The primary endpoint was the proportion of patients with a JIA ACR 30 flare at week 40 relative to week 16. JIA ACR 30 flare was defined as 3 or more of the 6 core outcome variables worsening by at least 30% with no more than 1 of the remaining variables improving by more than 30% relative to Week 16.

Tocilizumab treated patients experienced significantly fewer disease flares compared to placebo-treated patients (26% [21/82] versus 48% [39/81]; adjusted difference in proportions -21%, 95% CI: -35%, -8%).

During the withdrawal phase (Part II), more patients treated with tocilizumab showed JIA ACR 30/50/70 responses at Week 40 compared to patients withdrawn to placebo.

14.3 Systemic Juvenile Idiopathic Arthritis—Intravenous Administration

The efficacy of tocilizumab for the treatment of active SJIA was assessed in WA18221 (NCT00642460), a 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study. Patients treated with or without MTX, were randomized (tocilizumab:placebo = 2:1) to one of two treatment groups: 75 patients received tocilizumab infusions every two weeks at either 8 mg per kg for patients at or above 30 kg or 12 mg per kg for patients less than 30 kg and 37 were randomized to receive placebo infusions every two weeks. Corticosteroid tapering could occur from week six for patients who achieved a JIA ACR 70 response. After 12 weeks or at the time of escape, due to disease worsening, patients were treated with tocilizumab in the open-label extension phase at weight appropriate dosing.

The primary endpoint was the proportion of patients with at least 30% improvement in JIA ACR core set (JIA ACR 30 response) at Week 12 and absence of fever (no temperature at or above 37.5°C in the preceding 7 days). JIA ACR (American College of Rheumatology) responses are

defined as the percentage improvement (e.g., 30%, 50%, 70%) in 3 of any 6 core outcome variables compared to baseline, with worsening in no more than 1 of the remaining variables by 30% or more. Core outcome variables consist of physician global assessment, parent per patient global assessment, number of joints with active arthritis, number of joints with limitation of movement, erythrocyte sedimentation rate (ESR), and functional ability (childhood health assessment questionnaire-CHAQ).

Primary endpoint result and JIA ACR response rates at Week 12 are shown in [Table 7](#).

Table 7 Efficacy Findings at Week 12

	Tocilizumab N=75	Placebo N=37
Primary Endpoint: JIA ACR 30 response + absence of fever		
Responders	85%	24%
Weighted difference (95% CI)	62 (45, 78)	-
JIA ACR Response Rates at Week 12		
JIA ACR 30		
Responders	91%	24%
Weighted difference ^a (95% CI) ^b	67 (51, 83)	-
JIA ACR 50		
Responders	85%	11%
Weighted difference ^a (95% CI) ^b	74 (58, 90)	-
JIA ACR 70		
Responders	71%	8%
Weighted difference ^a (95% CI) ^b	63 (46, 80)	-

^a The weighted difference is the difference between the tocilizumab and Placebo response rates, adjusted for the stratification factors (weight, disease duration, background oral corticosteroid dose and background methotrexate use).

^b CI: confidence interval of the weighted difference.

The treatment effect of tocilizumab was consistent across all components of the JIA ACR response core variables. JIA ACR scores and absence of fever responses in the open label extension were consistent with the controlled portion of the study (data available through 44 weeks).

Systemic Features

Of patients with fever or rash at baseline, those treated with tocilizumab had fewer systemic features; 35 out of 41 (85%) became fever free (no temperature recording at or above 37.5°C in the preceding 14 days) compared to 5 out of 24 (21%) of placebo-treated patients, and 14 out of

22 (64%) became free of rash compared to 2 out of 18 (11%) of placebo-treated patients. Responses were consistent in the open label extension (data available through 44 weeks).

Corticosteroid Tapering

Of the patients receiving oral corticosteroids at baseline, 8 out of 31 (26%) placebo and 48 out of 70 (69%), tocilizumab patients achieved a JIA ACR 70 response at week 6 or 8 enabling corticosteroid dose reduction. Seventeen (24%) tocilizumab patients versus 1 (3%) placebo patient were able to reduce the dose of corticosteroid by at least 20% without experiencing a subsequent JIA ACR 30 flare or occurrence of systemic symptoms to week 12. In the open label portion of the study, by week 44, there were 44 out of 103 (43%) tocilizumab patients off oral corticosteroids. Of these 44 patients 50% were off corticosteroids 18 weeks or more.

Health Related Outcomes

Physical function and disability were assessed using the Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI). Seventy-seven percent (58 out of 75) of patients in the tocilizumab treatment group achieved a minimal clinically important improvement in CHAQ-DI (change from baseline of ≥ 0.13 units) at week 12 compared to 19% (7 out of 37) in the placebo treatment group.

16 HOW SUPPLIED/STORAGE AND HANDLING

TOFIDENCE (tocilizumab-bavi) injection is a preservative-free, sterile, clear to opalescent, colorless to light yellow solution. TOFIDENCE is supplied as 80 mg/4 mL (NDC 64406-024-01), 200 mg/10 mL (NDC 64406-022-01), and 400 mg/20 mL (NDC 64406-023-01) individually packaged 20 mg/mL single-dose vials for further dilution prior to intravenous infusion.

Storage and Handling: Do not use beyond expiration date on the container or package. TOFIDENCE must be refrigerated at 36°F to 46°F (2°C to 8°C). Do not freeze. Protect the vials from light by storage in the original package until time of use.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- **Serious Infections**

Inform patients that TOFIDENCE may lower their resistance to infections [see *Warnings and Precautions (5.1)*]. Instruct the patient of the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.

- **Gastrointestinal Perforation**

Inform patients that some patients who have been treated with TOFIDENCE have had serious side effects in the stomach and intestines [see *Warnings and Precautions (5.2)*]. Instruct the patient of the importance of contacting their doctor immediately when symptoms of severe, persistent abdominal pain appear to assure rapid evaluation and appropriate treatment.

- **Hypersensitivity and Serious Allergic Reactions**

Inform patients that some patients who have been treated with TOFIDENCE have developed serious allergic reactions, including anaphylaxis [see *Warnings and Precautions (5.6)*]. Advise patients to seek immediate medical attention if they experience any symptom of serious allergic reactions.

Pregnancy

Inform female patients of reproductive potential that TOFIDENCE may cause fetal harm and to inform their prescriber of a known or suspected pregnancy [see *Use in Specific Populations (8.1)*].

TOFIDENCE™ (tocilizumab-bavi)

Manufactured by:

Biogen MA Inc.

Cambridge, MA 02142

U.S. License No.: 2344

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Medication Guide

TOFIDENCE™ (TOE-FIH-DENCE) (tocilizumab-bavi) injection for intravenous use

What is the most important information I should know about TOFIDENCE?

TOFIDENCE can cause serious side effects including:

- 1. Serious Infections.** TOFIDENCE is a medicine that affects your immune system. TOFIDENCE can lower the ability of your immune system to fight infections. Some people have serious infections while taking TOFIDENCE, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections. Your healthcare provider should assess you for TB before starting TOFIDENCE.

Your healthcare provider should monitor you closely for signs and symptoms of TB during treatment with TOFIDENCE.

- You should not start taking TOFIDENCE if you have any kind of infection unless your healthcare provider says it is okay.

Before starting TOFIDENCE, tell your healthcare provider if you:

- think you have an infection or have symptoms of an infection, with or without a fever, such as:
 - sweating or chills
 - shortness of breath
 - warm, red, or painful skin or sores on your body
 - feel very tired
 - muscle aches
 - blood in phlegm
 - diarrhea or stomach pain
 - cough
 - weight loss
 - burning when you urinate or urinating more often than normal
- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidiomycosis, or blastomycosis). These infections may happen or become more severe if you use TOFIDENCE. Ask your healthcare provider, if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B.

After starting TOFIDENCE, call your healthcare provider right away if you have any symptoms of an infection. TOFIDENCE can make you more likely to get infections or make worse any infection that you have.

2. Tears (perforation) of the stomach or intestines.

- Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking TOFIDENCE get tears in their stomach or intestine. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
- Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away, and a change in your bowel habits.

3. Liver problems (Hepatotoxicity):

Some people have experienced serious life-threatening liver problems, which required a liver transplant or led to death. Your healthcare provider may tell you to stop taking TOFIDENCE if you develop new or worse liver problems during treatment with TOFIDENCE. Tell your healthcare provider right away if you have any of the following symptoms:

- feeling tired (fatigue)
- lack of appetite for several days or longer (anorexia)
- yellowing of your skin or the whites of your eyes (jaundice)
- abdominal swelling and pain on the right side of your stomach-area
- light colored stools
- weakness
- nausea and vomiting
- confusion
- dark “tea-colored” urine

4. Changes in certain laboratory test results. Your healthcare provider should do blood tests before you start receiving TOFIDENCE. If you have rheumatoid arthritis (RA) your healthcare provider should do blood tests every 4 to 8 weeks after you start receiving TOFIDENCE for the first 6 months and then every 3 months after that. If you have polyarticular juvenile idiopathic arthritis (PJIA) you will have blood tests done every 4 to 8 weeks during treatment. If you have systemic juvenile idiopathic arthritis (SJIA) you will have blood tests done every 2 to 4 weeks during treatment. These blood tests are to check for the following side effects of TOFIDENCE:

- low neutrophil count. Neutrophils are white blood cells that help the body fight off bacterial infections.
- low platelet count. Platelets are blood cells that help with blood clotting and stop bleeding.
- increase in certain liver function tests.
- increase in blood cholesterol levels. You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider should do blood tests to check your cholesterol levels 4 to 8 weeks after you start receiving TOFIDENCE.

Your healthcare provider will determine how often you will have follow-up blood tests. Make sure you get all your follow-up blood tests done as ordered by your healthcare provider. You should not receive TOFIDENCE if your neutrophil or platelet counts are too low or your liver function tests are too high.

Your healthcare provider may stop your TOFIDENCE treatment for a period of time or change your dose of medicine if needed because of changes in these blood test results.

5. Cancer. TOFIDENCE may increase your risk of certain cancers by changing the way your immune system works. Tell your healthcare provider if you have ever had any type of cancer.

See “**What are the possible side effects with TOFIDENCE?**” for more information about side effects.

What is TOFIDENCE?

TOFIDENCE is a prescription medicine called an Interleukin-6 (IL-6) receptor antagonist. TOFIDENCE is used:

- To treat adults with moderately to severely active rheumatoid arthritis (RA), after at least one other medicine called a Disease-Modifying Anti-Rheumatic Drug (DMARD) has been used and did not work well.
- To treat people with active PJIA ages 2 and above.
- To treat people with active SJIA ages 2 and above.

It is not known if TOFIDENCE is safe and effective in children with PJIA or SJIA under 2 years of age or in children with conditions other than PJIA or SJIA.

Do not take TOFIDENCE: if you are allergic to tocilizumab products, or any of the ingredients in TOFIDENCE. See the end of this Medication Guide for a complete list of ingredients in TOFIDENCE.

Before you receive TOFIDENCE, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection. See “**What is the most important information I should know about TOFIDENCE?**”
- have liver problems.
- have any stomach-area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines.
- have had a reaction to tocilizumab or any of the ingredients in TOFIDENCE before.
- have or had a condition that affects your nervous system, such as multiple sclerosis.
- have recently received or are scheduled to receive a vaccine:
 - All vaccines should be brought up-to-date before starting TOFIDENCE, unless urgent treatment initiation is required.
 - People who take TOFIDENCE should not receive live vaccines.
 - People taking TOFIDENCE can receive non-live vaccines.
- plan to have surgery or a medical procedure.
- are pregnant or plan to become pregnant or are pregnant. TOFIDENCE may harm your unborn baby. Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with TOFIDENCE.
- are breastfeeding or plan to breastfeed. It is not known if TOFIDENCE passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take TOFIDENCE.

Tell your healthcare provider about all of the medicines you take, including prescription, over-the-counter medicines, vitamins and herbal supplements. TOFIDENCE and other medicines may affect each other causing side effects. Especially tell your healthcare provider if you take:

- any other medicines to treat your RA. You should not take etanercept (Enbrel), adalimumab (Humira), infliximab (Remicade), rituximab (Rituxan), abatacept (Orencia), anakinra (Kineret), certolizumab (Cimzia), or golimumab (Simponi), while you are taking TOFIDENCE. Taking TOFIDENCE with these medicines may increase your risk of infection.
- medicines that affect the way certain liver enzymes work. Ask your healthcare provider if you are not sure if your medicine is one of these.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How will I receive TOFIDENCE?

Into a vein (IV or intravenous infusion) for Rheumatoid Arthritis, PJIA, or SJIA:

- If your healthcare provider prescribes TOFIDENCE as an IV infusion, you will receive TOFIDENCE from a healthcare provider through a needle placed in a vein in your arm. The infusion will take about 1 hour to give you the full dose of medicine.
- For rheumatoid arthritis or PJIA you will receive a dose of TOFIDENCE about every 4 weeks.
- For SJIA you will receive a dose of TOFIDENCE about every 2 weeks.
- While taking TOFIDENCE, you may continue to use other medicines that help treat your rheumatoid arthritis, PJIA, or SJIA such as methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as instructed by your healthcare provider.
- Keep all of your follow-up appointments and get your blood tests as ordered by your healthcare provider.

What are the possible side effects with TOFIDENCE? TOFIDENCE can cause serious side effects, including:

- See **“What is the most important information I should know about TOFIDENCE?”**
- **Hepatitis B infection** in people who carry the virus in their blood. If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus may become active while you use TOFIDENCE. Your healthcare provider may do blood tests before you start treatment with TOFIDENCE and while you are using TOFIDENCE. Tell your healthcare provider if you have any of the following symptoms of a possible hepatitis B infection:
 - feel very tired
 - vomiting
 - chills
 - dark urine
 - skin or eyes look yellow
 - clay-colored bowel movements
 - stomach discomfort
 - skin rash
 - little or no appetite
 - fevers
 - muscle aches
- **Serious Allergic Reactions.** Serious allergic reactions, including death, can happen with TOFIDENCE. These reactions can happen with any infusion of TOFIDENCE, even if they did not occur with an earlier infusion. Tell your healthcare provider before your next dose if you had hives, rash or flushing after your injection. Seek medical attention right away if you have any of the following signs of a serious allergic reaction:
 - shortness of breath or trouble breathing
 - swelling of the lips, tongue, or face chest pain
 - feeling dizzy or faint
 - moderate or severe abdominal pain or vomiting
- **Nervous system problems.** While rare, Multiple Sclerosis has been diagnosed in people who take TOFIDENCE. It is not known what effect TOFIDENCE may have on some nervous system disorders.

The most common side effects of TOFIDENCE include:

- upper respiratory tract infections (common cold, sinus infections)
- headache
- increased blood pressure (hypertension)
- injection site reactions

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Biogen MA Inc. at 1-866-633-4636 .

General information about the safe and effective use of TOFIDENCE.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not give TOFIDENCE to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TOFIDENCE that is written for health professionals.

What are the ingredients in TOFIDENCE?

Active ingredient: tocilizumab-bavi.

Inactive ingredients of Intravenous TOFIDENCE: arginine hydrochloride, histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose, and water for Injection.

TOFIDENCE is a trademark of Biogen MA Inc.

Manufactured by: **Biogen MA Inc., Cambridge, MA 02142**, U.S. License No.: 2344

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For more information call 1-866-633-4636.

Medication Guide has been approved by the U.S. Food and Drug Administration

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