Tofidence™
tocilizumab-bavi

Safety and Laboratory Monitoring Guide

Patients taking TOFIDENCE™ should be monitored for changes in lipids, hepatic transaminases, neutrophils, and platelets, as changes in these parameters were associated with treatment with tocilizumab products. Dosage modifications may be required.

Please note that while safety monitoring and laboratory tests were conducted in the TOFIDENCE Phase III trial, the data presented in this guide align to the Prescribing Information, and represent data generated during the Actemra® (tocilizumab) clinical program.*

*Actemra is a registered trademark of Genentech, Inc.

INDICATIONS

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).

Polyarticular Juvenile Idiopathic Arthritis (PJIA)

TOFIDENCE is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

Systemic Juvenile Idiopathic Arthritis (SJIA)

TOFIDENCE is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

SELECTED SAFETY 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. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate (MTX) 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.

CONTRAINDICATIONS

TOFIDENCE is contraindicated in patients with known hypersensitivity to tocilizumab products.

Please see Important Safety Information on pages 9-12 and full Prescribing Information, including Boxed Warning.

TOFIDENCE Dosing and Administration Guide[1]

General Dosing

General Dosing Information

- For patients with RA, PJIA, and SJIA, TOFIDENCE may be used alone or in combination with methotrexate: and for patients with RA, other DMARDs may be used. Avoid using TOFIDENCE with biological DMARDs
- TOFIDENCE is administered as a 60-minute single intravenous drip infusion. Do not administer as an intravenous push or bolus
- Obtain and assess baseline complete blood count (CBC) and liver function tests prior to treatment
- It is not recommended to initiate TOFIDENCE in patients with an absolute neutrophil count (ANC) below 2000 per mm^3, platelet count below 100,000 per mm^3, or who have alanine amniotransferase (ALT) or aspartate transaminase (AST) above 1.5x the upper limit of normal (ULN) *(5.3, 5.4)*
- In patients with RA, TOFIDENCE doses exceeding 800 mg/infusion are not recommended *(2.2, 12.3)*
- Hold TOFIDENCE treatment if a patient develops a serious infection until the infection is controlled

Rheumatoid Arthritis *(2.2)*

Recommended Adult Intravenous Dosage

- When used as monotherapy or in combination with DMARDs: starting on 4 mg/kg every 4 weeks
- Based on clinical response, increase to 8 mg/kg every 4 weeks

Polyarticular Juvenile Idiopathic Arthritis *(2.3)*

Recommended Intravenous PJIA Dosage

- Patients weighing <30 kg: 10 mg/kg every 4 weeks
- Patients weighing ≥30 kg: 8 mg/kg every 4 weeks

Systemic Juvenile Idiopathic Arthritis *(2.4)*

Recommended Intravenous SJIA Dosage

- Patients weighing <30 kg: 12 mg/kg every 2 weeks
- Patients weighing ≥30 kg: 8 mg/kg every 2 weeks

Monitoring Highlights:
Key Warnings and Precautions[1]

For the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs, patients 2 years and older with PJIA, and patients 2 years and older with SJIA.

Ongoing monitoring of your patient is important during the treatment of chronic disease. Some biologic agents used in the treatment of RA, PJIA, and SJIA have guidelines for the management of changes in laboratory values. Patients taking TOFIDENCE should be monitored for changes in lipids, hepatic transaminases, neutrophils, and platelets, as changes in these parameters were associated with treatment with tocilizumab products. Dosage modifications may be required.

Please see Important Safety Information on pages 9-12 and full Prescribing Information, including Boxed Warning.

LIPIDS

Assess before treatment initiation, then:
RA, PJIA, SJIA: 4-8 WEEKS FOLLOWING INITIATION *(5.4, 7.2)*

WARNINGS: Treatment with tocilizumab products was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol.

- Manage patients according to clinical guidelines (eg, National Cholesterol Educational Program [NCEP]) for the management of hyperlipidemia
- Prescribers should exercise caution when TOFIDENCE is coadministered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable (eg, oral contraceptives, lovastatin, atorvastatin)

A similar pattern of lipid elevations is noted in treatment with tocilizumab products in the PJIA and SJIA populations.

HDL=high-density lipoprotein; LDL=low-density lipoprotein.

LIVER FUNCTION TEST (ALT/AST)

Assess before treatment initiation, then:
RA: EVERY 4-8 WEEKS AFTER INITIATION AND EVERY 3 MONTHS THEREAFTER *(2.6, 5.3)*
PJIA: AT THE TIME OF THE SECOND ADMINISTRATION; THEN EVERY 4-8 WEEKS *(2.6, 5.3)*
SJIA: AT THE TIME OF THE SECOND ADMINISTRATION; THEN EVERY 2-4 WEEKS *(2.6, 5.3)*

WARNINGS: 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 (>5x 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 (eg, MTX) were used in combination with tocilizumab.

For patients with RA, obtain a liver test panel (ALT, 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 patients with RA with elevated transaminases ALT or AST >1.5x ULN. In patients who develop elevated ALT or AST >5x ULN, discontinue TOFIDENCE**. For recommended modifications based upon increase in transaminases, see *Dosage and Administration (2.6)*.

Monitoring Highlights:
Key Warnings and Precautions[1] (cont'd)

LIVER FUNCTION TEST (ALT/AST) (cont'd)

Measure liver function 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 (eg, ALT >3x the upper limit of the reference range, serum total bilirubin >2x 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 in treatment with tocilizumab products in the PJIA and SJIA populations.

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 below for patients with RA. If appropriate, dose modify or stop concomitant MTX and/or other medications and hold TOFIDENCE dosing until the clinical situation has been evaluated. For patients with PJIA and SJIA, the decision to discontinue TOFIDENCE for a laboratory abnormality should be based upon the medical assessment of the individual patient.

Liver Enzyme Abnormalities *[see Warnings and Precautions (5.3, 5.4)]*

Lab Value	Recommendation for RA
>1x to 3x ULN	**Dose** modify concomitant DMARDs if appropriate. For persistent increases in this range: • **Reduce** dose to 4 mg/kg or hold TOFIDENCE until ALT or AST has normalized
>3x to 5x ULN (confirmed by repeat testing)	**Hold** TOFIDENCE dosing until <3x ULN and follow recommendations above for >1x to 3x ULN. For persistent increases >3x ULN, **discontinue** TOFIDENCE.
>5x ULN	**Discontinue** TOFIDENCE.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; DMARD=disease-modifying antirheumatic drug; MTX=methotrexate; ULN=upper limit of normal.

Monitoring Highlights:
Key Warnings and Precautions[1] (cont'd)

NEUTROPHILS

Assess before treatment initiation, then:
RA: 4-8 WEEKS FOLLOWING INITIATION; THEN AT 3-MONTH INTERVALS *(2.6, 5.4)*
PJIA: AT THE TIME OF THE SECOND ADMINISTRATION; THEN EVERY 4-8 WEEKS *(2.6, 5.4)*
SJIA: AT THE TIME OF THE SECOND ADMINISTRATION; THEN EVERY 2-4 WEEKS *(2.6, 5.4)*

WARNINGS: 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 patients with RA with a low neutrophil count, ie, ANC <2000 per mm^3. In patients who develop an ANC <500 per mm^3, treatment is not recommended.**

A similar pattern of low neutrophil count is noted in treatment with tocilizumab products in the PJIA and SJIA populations.

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

Low ANC *[see Warnings and Precautions (5.4)]*

Lab Value (cells per mm^3)	Recommendation for RA
ANC >1000	**Maintain** dose.
ANC 500 to 1000	**Hold** TOFIDENCE dosing. When ANC is >1000 cells per mm^3: • **Resume** TOFIDENCE at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC <500	**Discontinue** TOFIDENCE.

ANC=absolute neutrophil count.

Monitoring Highlights:
Key Warnings and Precautions[1] (cont'd)

PLATELETS

Assess before treatment initiation, then:

RA: 4-8 WEEKS FOLLOWING INITIATION; THEN AT 3-MONTH INTERVALS *(2.6, 5.4)*

PJIA: AT THE TIME OF THE SECOND ADMINISTRATION; THEN EVERY 4-8 WEEKS *(2.6, 5.4)*

SJIA: AT THE TIME OF THE SECOND ADMINISTRATION; THEN EVERY 2-4 WEEKS *(2.6, 5.4)*

WARNINGS: 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. **It is not recommended to initiate TOFIDENCE treatment in patients with RA with a platelet count <100,000 per mm^3. In patients who develop a platelet count <50,000 per mm^3, treatment is not recommended.**

A similar pattern of low platelet count is noted in treatment with tocilizumab products in the PJIA and SJIA populations.

Dose reduction of tocilizumab products has not been studied in the PJIA and SJIA populations. Dose interruptions of TOFIDENCE are recommended for low platelet counts in patients with PJIA and SJIA at levels similar to what is outlined below 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. For patients with PJIA and SJIA, the decision to discontinue TOFIDENCE for a laboratory abnormality should be based upon the medical assessment of the individual patient.

Low Platelet Count *[see Warnings and Precautions (5.4)]*

Lab Value (cells per mm^3)	Recommendation for RA
50,000 to 100,000	**Hold** TOFIDENCE dosing. When platelet count is >100,000 cells per mm^3: • **Resume** TOFIDENCE at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
<50,000	**Discontinue** TOFIDENCE.

Patients Taking TOFIDENCE May Experience Increased Lipids,

Which Can Be Managed According to Clinical Guidelines[1]

Elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were first assessed at 6 weeks following initiation of TOFIDENCE in the controlled 24-week RA clinical trials.

Increases were observed at this time point and remained stable thereafter.

Increases in triglycerides to levels above 500 mg/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/dL in the tocilizumab 4 mg/kg + DMARD arm, 20 mg/dL in the tocilizumab 8 mg/kg + DMARD arm, and 25 mg/dL in tocilizumab 8 mg/kg monotherapy arm
- Mean HDL increased by 3 mg/dL in the tocilizumab 4 mg/kg + DMARD arm, 5 mg/dL in the tocilizumab 8 mg/kg + DMARD arm, and 4 mg/dL in the tocilizumab 8 mg/kg monotherapy arm
- Mean LDL/HDL ratio increased by an average of 0.14 in the tocilizumab 4 mg/ kg + DMARD arm, 0.15 in the tocilizumab 8 mg/kg + DMARD arm, and 0.26 in tocilizumab 8 mg/kg monotherapy arm
- 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 controlled 24-week clinical trials.

Routine Monitoring

Assess lipid parameters approximately 4 to 8 weeks following initiation of TOFIDENCE treatment. Manage patients according to clinical guidelines for the treatment of patient's hyperlipidemia. Exercise caution when coadministering TOFIDENCE with CYP3A4 substrate drugs where decrease in effectiveness is undesirable (eg, oral contraceptives, lovastatin, atorvastatin). The effect of TOFIDENCE on CYP450 enzyme activity may persist for several weeks after stopping therapy.

TOFIDENCE Clinical Trials:

Summary of Patterns of Neutropenia in Patients With Grade 3 or 4 Neutropenia[1]*

Patterns of Neutropenia in Adult Patients With RA With a Grade 3 or 4 Neutrophil Count in 24-Week Randomized Controlled Trials (N=4009)

	4 mg/kg TOFIDENCE + DMARD (%)	8 mg/kg TOFIDENCE + DMARD (%)	PLACEBO + DMARD (%)
Neutrophil Count Reduction <1000/mm^3	1.8	3.4	0.1
Neutrophil Count Reduction <500/mm^3	0.4	0.3	0.1

It is not recommended to initiate TOFIDENCE treatment in patients with RA with a low neutrophil count, ie, ANC <2000/mm^3. In patients who develop an ANC <500/mm^3, treatment is not recommended. Monitor neutrophils 4 to 8 weeks after treatment initiation and every 3 months thereafter.

There was no clear relationship between decreases in neutrophils below 1000/mm^3 and the occurrence of serious infections

Patients With PJIA (N=188)

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

Monitor neutrophils at the time of the second administration and every 4 to 8 weeks thereafter.

Patients With SJIA (N=112)

- During routine laboratory monitoring in the 12-week controlled phase, a decrease in neutrophil counts below 1 × 10^9/L occurred in 7% of patients receiving TOFIDENCE, and in no patients in the placebo group
- In the open-label extension (average 73 weeks), a decreased neutrophil count occurred in 17% of patients receiving TOFIDENCE

Monitor neutrophils at the time of the second administration and every 2 to 4 weeks thereafter.

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

*Grade 3=severe adverse event; Grade 4=life-threatening or disabling adverse event according to the Common Terminology Criteria for Adverse Events.[2]
DMARD=disease-modifying anti-rheumatic drug.

Tofidence™ tocilizumab-bavi

INDICATIONS

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).

Polyarticular Juvenile Idiopathic Arthritis (PJIA)

TOFIDENCE is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

Systemic Juvenile Idiopathic Arthritis (SJIA)

TOFIDENCE is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

IMPORTANT SAFETY 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. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate (MTX) 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.

CONTRAINDICATIONS

TOFIDENCE is contraindicated in patients with known hypersensitivity to tocilizumab products.

WARNINGS AND PRECAUTIONS

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. 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.

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.

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.

Tofidence™
tocilizumab-bavi

IMPORTANT SAFETY INFORMATION (CONT'D)

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 upper limit of normal [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. 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.

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.

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 mm^3. In patients who develop an absolute neutrophil count less than 500 per mm^3 treatment is not recommended.

Monitor neutrophils 4 to 8 weeks after start of therapy and every 3 months thereafter.

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.

It is not recommended to initiate TOFIDENCE treatment in RA patients with a platelet count below 100,000 per mm^3. In patients who develop a platelet count less than 50,000 per mm^3 treatment is not recommended.

Monitor platelets 4 to 8 weeks after start of therapy and every 3 months thereafter.

Elevated Liver Enzymes

Refer to Hepatotoxicity. (See left column)

Lipid Abnormalities

Treatment with tocilizumab products was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol.

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.

Immunosuppression

The impact of treatment with tocilizumab products on the development of malignancies is not known but malignancies were observed in clinical studies. TOFIDENCE is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.

Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in association with tocilizumab products 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.

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.

Tofidence™
tocilizumab-bavi

IMPORTANT SAFETY INFORMATION (CONT'D)

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.

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.

Active Hepatic Disease and Hepatic Impairment

Treatment with TOFIDENCE is not recommended in patients with active hepatic disease or hepatic impairment.

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.

ADVERSE REACTIONS

Rheumatoid Arthritis

The tocilizumab-IV data in rheumatoid arthritis 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.

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.

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.

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.

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. 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.

Polyarticular Juvenile Idiopathic Arthritis

The safety of tocilizumab-IV was studied in 188 pediatric patients 2 to 17 years of age with PJIA 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.

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.

Tofidence™
tocilizumab-bavi

IMPORTANT SAFETY INFORMATION (CONT'D)

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.

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.

Systemic Juvenile Idiopathic Arthritis

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.

DRUG INTERACTIONS

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. Exercise caution when coadministering TOFIDENCE with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc.

Live Vaccines

Avoid use of live vaccines concurrently with TOFIDENCE.

USE IN PREGNANCY AND LACTATION

Based on animal data, there may be a potential risk to the fetus.

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.

Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to TOFIDENCE in utero.

The lack of clinical data during lactation precludes clear determination of the risk of tocilizumab products to an infant during lactation.

Please see full Prescribing Information, including Boxed Warning.

Tofidence™
tocilizumab-bavi

Tofidence™
tocilizumab-bavi

References: 1. TOFIDENCE Prescribing Information, Cambridge, MA: Biogen. **2.** US Common Terminology Criteria for Adverse Events (CTCAE): Version 5.0. National Institutes of Health, National Cancer Institute, US Dept of Health and Human Services; 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed January 18, 2023.

Please see Important Safety Information on pages 9-12 and full Prescribing Information, including Boxed Warning.

225 Binney Street, Cambridge, MA 02142