Tofidence™
tocilizumab-bavi

Safety and Laboratory Monitoring Guide

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) IV clinical program.*

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Patients taking TOFIDENCE™ (tocilizumab-bavi) injection, for intravenous use, 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 throughout and full Prescribing Information, including **Boxed Warning,** below.

*Actemra is a registered trademark of Chugai Seiyaku Kabushiki Kaisha Corp., a member of the Roche Group.
IV=intravenous.

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

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).

Giant Cell Arteritis (GCA)

TOFIDENCE™ (tocilizumab-bavi) is indicated for the treatment of giant cell arteritis in adult patients.

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.

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.

Coronavirus Disease 2019 (COVID-19)

TOFIDENCE™ (tocilizumab-bavi) is indicated for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adult patients who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

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, except those with COVID-19, 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.

Please see Important Safety Information on pages 9-11 and full Prescribing Information, including **Boxed Warning.**

TOFIDENCE Dosing and Administration Guide[1]

These highlights are from the US TOFIDENCE (tocilizumab-bavi) injection, for intravenous use, Prescribing Information and do not include all the information needed to use TOFIDENCE safely and effectively. See corresponding sections, shown in parentheses throughout, in the full Prescribing Information for additional information.

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 *(2, 2.1)*
- For GCA, TOFIDENCE can be used alone following discontinuation of glucocorticoids *(2.3)*
- Obtain and assess baseline complete blood count (CBC) and liver function tests prior to treatment
- TOFIDENCE is administered as a 60-minute single intravenous drip infusion. Do not administer as an intravenous push or bolus *(2.7)*
  - Laboratory monitoring is recommended due to potential consequences of treatment-related laboratory abnormalities in neutrophils, platelets, lipids, and liver function tests. Dosage modifications may be required *(2.8, 5.4)*
- RA, GCA, PJIA, and SJIA—It is recommended that TOFIDENCE not be initiated 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 aminotransferase (ALT) or aspartate aminotransferase (AST) above 1.5x the upper limit of normal (ULN) *(5.3, 5.4)*
- COVID-19—It is recommended that TOFIDENCE not be initiated in patients with an ANC below 1000 per mm^3, platelet count below 50,000 mm^3, or who have ALT or AST above 10x the ULN *(5.3, 5.4)*
- For patients with RA or COVID-19, TOFIDENCE doses exceeding 800 mg/infusion are not recommended *(2.2, 12.3)*
- For patients with GCA, TOFIDENCE doses exceeding 600 mg/infusion are not recommended *(2.3, 12.3)*
- For patients with RA, GCA, PJIA, SJIA, and COVID-19 at or above 30 kg, dilute to 100 mL in 0.9% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique *(2.7)*
- 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 *(2.7)*
- Hold TOFIDENCE treatment if a patient develops a serious infection until the infection is controlled *(2.8)*

Indication[1]	Dose	Dosing Schedule
Moderately to severely active RA in adult patients with inadequate response to one or more DMARDs *(2.2)*	Starting at 4 mg/kg followed by an increase to 8 mg/kg based on clinical response*	Every 4 weeks
GCA *(2.3)* Adult patients	6 mg/kg	Every 4 weeks, in combination with a tapering course of glucocorticoids†
PJIA (active) *(2.4)* Patients 2 years of age and older	Patients weighing <30 kg: 10 mg/kg	Every 4 weeks
	Patients weighing ≥30 kg: 8 mg/kg	Every 4 weeks
SJIA (active) *(2.5)* Patients 2 years of age and older	Patients weighing <30 kg: 12 mg/kg	Every 2 weeks
	Patients weighing ≥30 kg: 8 mg/kg	Every 2 weeks
Hospitalized adult patients with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO *(2.6)*	8 mg/kg	Single dose, one additional dose after 8 hours if needed‡

DMARD=disease-modifying anti-rheumatic drug; ECMO=extracorporeal membrane oxygenation.

*When used in combination with DMARDs or as monotherapy.
†TOFIDENCE can be used alone following discontinuation of glucocorticoids.
‡If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of TOFIDENCE may be administered at least 8 hours after the initial infusion.

Please see Important Safety Information on pages 9-11 and full Prescribing Information, including **Boxed Warning.**

Tofidence™ tocilizumab-bavi

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, adults with GCA, patients 2 years and older with active PJIA, patients 2 years and older with active SJIA, and hospitalized adult patients with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

Ongoing monitoring of your patient is important during the treatment of chronic disease. Some biologic agents used in the treatment of RA, GCA, PJIA, SJIA, and COVID-19 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 9-11 and full Prescribing Information, including **Boxed Warning**.

Baseline Laboratory Evaluation Prior to Treatment: Obtain and assess baseline complete blood count (CBC) and liver function tests prior to treatment. *(2.1)*

LIPIDS

Monitoring, and see below:
RA and GCA: 4-8 WEEKS FOLLOWING INITIATION *(5.4)*
PJIA and SJIA: MONITOR LIPIDS AS ABOVE FOR APPROVED ADULT INDICATIONS *[see Dosage and Administration (2.8)]*

WARNINGS: Treatment with tocilizumab products was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol. *(5.4)*

- Assess lipid parameters approximately 4 to 8 weeks following initiation of TOFIDENCE therapy *(5.4)*
- Subsequently, manage patients according to clinical guidelines (eg, National Cholesterol Educational Program [NCEP]) for the management of hyperlipidemia *(5.4)*
- Prescribers should exercise caution when TOFIDENCE is coadministered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable (oral contraceptives, lovastatin, atorvastatin, etc) *(7.2)*

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

LIVER FUNCTION TESTS

Assess before treatment initiation, then:
RA and GCA: EVERY 4-8 WEEKS AFTER INITIATION FOR THE FIRST 6 MONTHS AND EVERY 3 MONTHS THEREAFTER *(2.8, 5.3)*
PJIA: AT THE TIME OF THE SECOND ADMINISTRATION; THEN EVERY 4-8 WEEKS *(2.8, 5.3)*
SJIA: AT THE TIME OF THE SECOND ADMINISTRATION; THEN EVERY 2-4 WEEKS *(2.8, 5.3)*
COVID-19: DURING TREATMENT *(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, 6.4)]*. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (eg, MTX) were used in combination with tocilizumab.

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

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

LIVER FUNCTION TESTS (cont'd)

For patients with RA or GCA, 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 or GCA 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 (2.8)*.

Patients hospitalized with COVID-19 may have elevated ALT or AST levels. Multi-organ failure with involvement of the liver is recognized as a complication of severe COVID-19. The decision to administer TOFIDENCE should balance the potential benefit of treating COVID-19 against the potential risks of acute treatment with TOFIDENCE. It is not recommended to initiate TOFIDENCE treatment in COVID-19 patients with elevated ALT or AST above 10x ULN. Monitor ALT and AST during treatment.

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. 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.

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 and GCA. 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	Recommendation for GCA
>1x to 3x ULN	**Dose modify** concomitant DMARDs if appropriate. For persistent increases in this range: • **For patients receiving intravenous TOFIDENCE, reduce** dose to 4 mg/kg or hold TOFIDENCE until ALT or AST has normalized	**Dose modify** immunomodulatory agents if appropriate. For persistent increases in this range: • **For patients receiving intravenous TOFIDENCE, hold** TOFIDENCE until ALT or AST have 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.	**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.	**Discontinue** TOFIDENCE.

MTX=methotrexate; ULN=upper limit of normal.

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

NEUTROPHILS

Assess before treatment initiation, then:

RA and GCA: 4-8 WEEKS FOLLOWING INITIATION; THEN AT 3-MONTH INTERVALS *(2.8, 5.4)*

PJIA: AT THE TIME OF THE SECOND ADMINISTRATION; THEN EVERY 4-8 WEEKS *(2.8, 5.4)*

SJIA: AT THE TIME OF THE SECOND ADMINISTRATION; THEN EVERY 2-4 WEEKS *(2.8, 5.4)*

COVID-19: NEUTROPHILS SHOULD BE MONITORED *(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 or GCA 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.**

It is not recommended to initiate TOFIDENCE treatment in patients with COVID-19 with an ANC <1000 per mm^3. Neutrophils should be monitored.

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 and GCA. 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	Recommendation for GCA
ANC >1000	**Maintain** dose.	**Maintain** dose.
ANC 500 to 1000	**Hold** TOFIDENCE dosing. When ANC is >1000 cells per mm^3: • **For patients receiving intravenous TOFIDENCE, resume** TOFIDENCE at 4 mg/kg and increase to 8 mg/kg as clinically appropriate	**Hold** TOFIDENCE dosing. When ANC >1000 cells per mm^3: • **For patients receiving intravenous TOFIDENCE, resume** TOFIDENCE at 6 mg/kg
ANC <500	**Discontinue** TOFIDENCE.	**Discontinue** TOFIDENCE.

ANC=absolute neutrophil count.

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

PLATELETS

Assess before treatment initiation, then:

RA and GCA: 4-8 WEEKS FOLLOWING INITIATION; THEN AT 3-MONTH INTERVALS *(2.8, 5.4)*

PJIA: AT THE TIME OF THE SECOND ADMINISTRATION; THEN EVERY 4-8 WEEKS *(2.8, 5.4)*

SJIA: AT THE TIME OF THE SECOND ADMINISTRATION; THEN EVERY 2-4 WEEKS *(2.8, 5.4)*

COVID-19: PLATELETS SHOULD BE MONITORED *(5.4)*

WARNINGS: Treatment with tocilizumab products was associated with a reduction in platelet counts. **It is not recommended to initiate TOFIDENCE treatment in patients with RA or GCA with a platelet count <100,000 per mm³. In patients who develop a platelet count <50,000 per mm³, treatment is not recommended.**

In patients with COVID-19 with a platelet count <50,000 per mm³, treatment is not recommended. Platelets should be monitored.

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

Lab Value (cells per mm³)	Recommendation for RA	Recommendation for GCA
50,000 to 100,000	**Hold** TOFIDENCE dosing. When platelet count is >100,000 cells per mm³: • **For patients receiving intravenous TOFIDENCE, resume** TOFIDENCE at 4 mg/kg and increase to 8 mg/kg as clinically appropriate	**Hold** TOFIDENCE dosing. When platelet count is >100,000 cells per mm³: • **For patients receiving intravenous TOFIDENCE, resume** TOFIDENCE at 6 mg/kg
<50,000	**Discontinue** TOFIDENCE.	**Discontinue** TOFIDENCE.

Patients Taking TOFIDENCE May Experience Increased Lipids[1]

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 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

Monitoring, then:
RA and GCA: 4-8 WEEKS FOLLOWING INITIATION *(5.4)*
PJIA and SJIA: MONITOR LIPIDS AS ABOVE FOR APPROVED ADULT INDICATIONS *[see Dosage and Administration (2.8)]*

WARNINGS: Treatment with tocilizumab products was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol. *(5.4)*

- Assess lipid parameters approximately 4 to 8 weeks following initiation of TOFIDENCE therapy *(5.4)*
- Subsequently, manage patients according to clinical guidelines (eg, National Cholesterol Educational Program [NCEP]) for the management of hyperlipidemia *(5.4)*
- Prescribers should exercise caution when TOFIDENCE is coadministered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable (oral contraceptives, lovastatin, atorvastatin, etc) *(7.2)*

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

The effect of tocilizumab products on CYP450 enzyme activity may persist for several weeks after stopping therapy *[see Clinical Pharmacology (12.3)]*.

Tocilizumab IV Clinical Trial Experience:

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

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

Tocilizumab IV All-Exposure Population (N=4,009)

	4 mg/kg tocilizumab-IV + DMARD (%)	8 mg/kg tocilizumab-IV + 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 or GCA 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.

In the 24-week, controlled clinical studies in RA, there was no clear relationship between decreases in neutrophils below 1000/mm^3 and the occurrence of serious infections

Adult Patients With GCA (N=24) *(6.2)*

- The overall safety profile observed for tocilizumab administered intravenously in patients with GCA was consistent with the known safety profile of tocilizumab

It is not recommended to initiate TOFIDENCE treatment in patients with GCA 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.

Patients With PJIA (N=188) *(6.3)*

- During routine laboratory monitoring in the tocilizumab-IV 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) *(6.4)*

- 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 in the tocilizumab-IV group, 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 in the tocilizumab-IV group

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

Adult Patients With COVID-19 (N=974) *(6.5)*

- The safety of tocilizumab in hospitalized COVID-19 patients was evaluated in a pooled safety population that includes patients enrolled in 3 studies (EMPACTA, COVACTA, and REMDACTA)
- Neutrophil counts <1000 cells/mcl occurred in 3.4% of patients who received tocilizumab, and in 0.5% of patients receiving placebo

It is not recommended to initiate TOFIDENCE treatment in patients with COVID-19 with an ANC <1000 per mm^3. Neutrophils should be monitored.

In patients with PJIA and SJIA, 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]

Tofidence™ tocilizumab-bavi

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

INDICATIONS

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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).

Giant Cell Arteritis (GCA)

TOFIDENCE™ (tocilizumab-bavi) is indicated for the treatment of giant cell arteritis in adult patients.

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.

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.

Coronavirus Disease 2019 (COVID-19)

TOFIDENCE™ (tocilizumab-bavi) is indicated for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adult patients who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

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, except those with COVID-19, 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: see Boxed Warning

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.

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.

It is not recommended to initiate TOFIDENCE treatment in RA, GCA, PJIA and SJIA 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.

Patients hospitalized with COVID-19 may have elevated ALT or AST levels. Multi-organ failure with involvement of the liver is recognized as a complication of severe COVID-19. The decision to administer TOFIDENCE should balance the potential benefit of treating COVID-19 against the potential risks of acute treatment with TOFIDENCE. It is not recommended to initiate TOFIDENCE treatment in COVID-19 patients with elevated ALT or AST above 10x ULN.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury. If the patient is found to have abnormal liver tests, TOFIDENCE treatment should be interrupted. TOFIDENCE should only be restarted in patients with another explanation for the liver test abnormalities after normalization of the liver tests.

Changes in Laboratory Parameters

Laboratory monitoring is recommended due to potential consequences of treatment-related laboratory abnormalities in neutrophils, platelets, lipids, and liver function tests. Dosage modifications may be required.

Neutropenia

Treatment with tocilizumab products was associated with a higher incidence of neutropenia. It is not recommended to initiate TOFIDENCE treatment in RA, GCA, PJIA and SJIA 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.

It is not recommended to initiate TOFIDENCE treatment in COVID-19 patients with an ANC less than 1000 per mm^3.

Thrombocytopenia

Treatment with tocilizumab products was associated with a reduction in platelet counts. It is not recommended to initiate TOFIDENCE treatment in RA, GCA, PJIA and SJIA 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.

In COVID-19 patients with a platelet count less than 50,000 per mm^3, treatment is not recommended.

Please see full Prescribing Information, including **Boxed Warning.**

IMPORTANT SAFETY INFORMATION (Cont'd)

Changes in Laboratory Parameters (cont'd)

Elevated Liver Enzymes

It is not recommended to initiate TOFIDENCE treatment in patients with elevated transaminases ALT or AST >1.5x ULN. In patients who develop ALT or AST >5x ULN, treatment is not recommended.

It is not recommended to initiate TOFIDENCE treatment in COVID-19 patients with elevated ALT or AST >10x ULN.

Lipid Abnormalities

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

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. In addition, serious cutaneous reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported in patients with autoinflammatory conditions treated with tocilizumab products. TOFIDENCE for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. If a hypersensitivity reaction occurs, immediately discontinue TOFIDENCE; treat promptly and monitor until signs and symptoms resolve.

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.

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 or on the effectiveness of vaccination in patients receiving tocilizumab products. Patients should be brought up to date on all recommended vaccinations prior to initiation of TOFIDENCE therapy, if possible.

ADVERSE REACTIONS

Rheumatoid Arthritis

The most common serious adverse reactions were serious infections. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. In the tocilizumab-IV monotherapy clinical study, the rate of serious infections was 3.6 per 100 patient years in the tocilizumab group and 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 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.

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).

In the 5 Phase III clinical trials, the most common adverse reactions (≥5% of patients treated with tocilizumab-IV) in the 24-week Phase 3 Controlled Study Population were:

	Tocilizumab 8 mg per kg MONOTHERAPY	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 %
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

Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay.

Giant Cell Arteritis

The overall safety profile observed for tocilizumab administered intravenously in GCA patients was generally consistent with the known safety profile of tocilizumab.

Polyarticular Juvenile Idiopathic Arthritis

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-IV (12.2 per 100 patient years) compared to patients weighing at or above 30 kg, treated with 8 mg/kg tocilizumab-IV (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-IV (21%) compared to patients weighing at or above 30 kg, treated with 8 mg/kg tocilizumab-IV (8%).

IMPORTANT SAFETY INFORMATION (Cont'd)

Polyarticular Juvenile Idiopathic Arthritis (cont'd)

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.

Systemic Juvenile Idiopathic Arthritis

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

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.

Coronavirus Disease 2019 (COVID-19)

The safety of tocilizumab in hospitalized COVID-19 patients was evaluated in a pooled safety population that includes patients enrolled in EMPACTA, COVACTA, AND REMDACTA.

The analysis of adverse reactions included a total of 974 patients exposed to tocilizumab.

Adverse Reaction	Tocilizumab 8 mg per kg N = 974 (%)	Placebo N = 483 (%)
Hepatic Transaminases increased	10%	8%
Constipation	9%	8%
Urinary tract infection	5%	4%
Hypertension	4%	1%
Hypokalaemia	4%	3%
Anxiety	4%	2%
Diarrhea	4%	2%
Insomnia	4%	3%
Nausea	3%	2%

In the pooled safety population, the rates of infection/serious infection events were 30%/19% in patients receiving tocilizumab versus 32%/23% receiving placebo.

Laboratory Abnormalities

In the pooled safety population of EMPACTA, COVACTA, and REMDACTA, neutrophil counts <1000 cells/mcl occurred in 3.4% of patients who received tocilizumab and 0.5% of patients who received placebo. Platelet counts <50,000 cells/mcl occurred in 3.2% of patients who received tocilizumab and 1.5% of patients who received placebo. ALT or AST at or above 5x ULN occurred in 11.7% of patients who received tocilizumab and 9.9% of patients who received placebo.

DRUG INTERACTIONS

In GCA patients, no effect of concomitant corticosteroid on tocilizumab exposure was observed.

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.

USE IN PREGNANCY

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.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Biogen MA Inc. at 1-877-422-8360.

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 September 5, 2024.

Please see Important Safety Information on pages 9-11 and full Prescribing Information, including **Boxed Warning.**

225 Binney Street, Cambridge, MA 02142