Tofidence™
tocilizumab-bavi

Access and Reimbursement Guide

Information on How to Navigate the Access and Reimbursement Process

TOFIDENCE™ (tocilizumab-bavi) injection, for IV use, is an FDA-approved biosimilar to Actemra® (tocilizumab).[1*†]

*A 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.[1]
†Actemra is a registered trademark of Genentech, Inc.

FDA=US Food and Drug Administration; IV=intravenous.

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.

Please see Important Safety Information on pages 17-20 and full Prescribing Information, including Boxed Warning.

Contents

Steps to Access

Before Administration

Benefits Investigation

Complete a benefits investigation to determine if a prior authorization (PA) is required and identify the following components:

- Coverage requirements, including PA and/or medical documentation, referral restrictions, and observation stay rules
- Patient out-of-pocket (OOP) costs, such as annual deductible vs amount met to date, coinsurance and/or copay, and annual OOP maximum vs amount met to date
- Billing guidelines, such as documentation requirements when submitting a claim and Healthcare Common Procedure Coding System (HCPCS) reporting requirements

PA

- To obtain a PA, contact the patient's payer(s) directly to submit necessary documentation such as PA, letters of medical necessity, out-of-state and/or out-of-network exception requests, and related documentation
- If an authorization or exception request has been denied, the appeal process and timeline will likely be stated in the denial letter. The healthcare provider may wish to contact the payer for instructions if the next steps in the process are not documented

IMPORTANT SAFETY INFORMATION (Cont'd)

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.

Steps to Access (cont'd)

After Administration

Submit a claim for reimbursement, track payer remittance, and evaluate responsiveness in addressing reimbursement issues

Did the claim go through? Monitor payer remittance for the submitted claim(s)

- Submit appeal with required documentation within filing timelines if the claim is denied
- Submit eligible OOP expenses to copay assistance or charitable funding programs, if applicable

Schedule the patient's next appointment

- Make sure to verify patient benefits before scheduling the next appointment

Refer to the recommended dosing during the patient's next appointment

For RA, PJIA, and SJIA, TOFIDENCE may be used alone or in combination with methotrexate; and in RA, other DMARDs may be used. Avoid using TOFIDENCE with biological DMARDs.[1]

Rheumatoid Arthritis (RA)[1]

Recommended Adult Intravenous Dosage

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

Polyarticular Juvenile Idiopathic Arthritis (PJIA)[1]

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 (SJIA)[1]

Recommended Intravenous SJIA Dosage

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

Laboratory monitoring and dose reduction is recommended for management of certain dose-related laboratory changes, including elevated liver enzymes, neutropenia, and thrombocytopenia (see Prescribing Information and Guidance Document).

IMPORTANT SAFETY INFORMATION (Cont'd)
WARNINGS AND PRECAUTIONS (Cont'd)
Serious Infections (cont'd)
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

Please see Important Safety Information on pages 17-20 and full Prescribing Information, including Boxed Warning.

Coverage, Coding, and Reimbursement

Biosimilar Reimbursement

TOFIDENCE is reimbursed using the buy-and-bill method, in which providers purchase the drug and bill to insurers after the patient receives the medication (as opposed to the patient receiving drugs directly from the pharmacy). Biosimilars are generally reimbursed under Medicare Part B at average sales price (ASP) +6% of the reference product's ASP.[2,3] As of October 1, 2022, the Centers for Medicare & Medicaid Services (CMS) has put in place a temporary increase whereby qualifying* biosimilars will be reimbursed at ASP +8% of its reference product's ASP for a period of 5 years.[3] If the ASP is not available, then the biosimilar will be reimbursed at the wholesale acquisition cost (WAC) plus 3%.[4†] Actemra is the reference product for TOFIDENCE.[1]

*Qualifying biosimilars are those that have an ASP that is not more than the ASP of the associated reference biological product.[3] Non-qualifying biosimilars would be reimbursed at ASP +6% of reference product's ASP.[3]

†Medicare Part B reimbursement is subject to sequestration. In practice, the sequestration payments result in an approximately 1.6% reduction in the Medicare Part B reimbursement (2.0% x 80% of the reimbursement to the provider).[5] If the ASP is not available, then the biosimilar will be reimbursed at the WAC plus 3%.[4]

Relevant Codes for TOFIDENCE

When a patient has received TOFIDENCE, your practice or facility may submit a claim to the patient's insurance plan. Page 6 reviews the codes commonly associated with the administration of TOFIDENCE.

IMPORTANT SAFETY INFORMATION (Cont'd)
WARNINGS AND PRECAUTIONS (Cont'd)
Serious Infections (cont'd)
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.

Coverage, Coding, and Reimbursement (cont'd)

Sample Coding for TOFIDENCE IV Infusion[6]

Rheumatoid Arthritis (RA)

DESCRIPTION	CODE
Rheumatoid lung disease with rheumatoid arthritis	M05.10–M05.19
Rheumatoid vasculitis with rheumatoid arthritis	M05.20–M05.29
Rheumatoid heart disease with rheumatoid arthritis	M05.30–M05.39
Rheumatoid myopathy with rheumatoid arthritis	M05.40–M05.49
Rheumatoid polyneuropathy with rheumatoid arthritis	M05.50–M05.59
Rheumatoid arthritis with involvement of other organs and systems	M05.60–M05.69
Rheumatoid arthritis with rheumatoid factor without organ or systems involvement	M05.70–M05.79
Rheumatoid arthritis with rheumatoid factor of other specified site without organ or systems involvement	M05.7A
Other rheumatoid arthritis with rheumatoid factor	M05.80–M05.8A
Rheumatoid arthritis with rheumatoid factor, unspecified	M05.9
Rheumatoid arthritis without rheumatoid factor	M06.00–M06.09
Rheumatoid arthritis without rheumatoid factor, other specified site	M06.0A
Other specified rheumatoid arthritis	M06.80–M06.8A
Rheumatoid arthritis, unspecified	M06.9

Polyarticular Juvenile Idiopathic Arthritis (PJIA)

DESCRIPTION	CODE
Unspecified juvenile rheumatoid arthritis of unspecified site	M08.00
Juvenile rheumatoid polyarthritis (seronegative)	M08.3
Other juvenile arthritis, unspecified site	M08.80
Juvenile arthritis, unspecified, unspecified site	M08.90

Systemic Juvenile Idiopathic Arthritis (SJIA)

DESCRIPTION	CODE
Juvenile rheumatoid arthritis with systemic onset	M08.20–M08.29
Juvenile rheumatoid arthritis with systemic onset, unspecified site	M08.20
Juvenile rheumatoid arthritis with systemic onset, other specified site	M08.2A
Other juvenile arthritis, unspecified site	M08.80
Juvenile arthritis, unspecified, unspecified site	M08.90

IMPORTANT SAFETY INFORMATION (Cont'd)
WARNINGS AND PRECAUTIONS (Cont'd)
Serious Infections (cont'd)

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

Please see Important Safety Information on pages 17-20 and full Prescribing Information, including Boxed Warning.

Coverage, Coding, and Reimbursement (cont'd)

HCPCS II Codes for TOFIDENCE[7]

Coding System	Code	Description
HCPCS II Code	Q5133	Injection, tocilizumab-bavi (tofidence), biosimilar, 1 mg

One billable unit of TOFIDENCE is equivalent to 1 mg[7]

TOFIDENCE is currently available as[1]:

- 80 mg/4 mL
- 200 mg/10 mL
- 400 mg/20 mL

All coding and documentation requirements should be confirmed with each payer before submitting a claim for reimbursement.

HCPCS=Healthcare Common Procedure Coding System.

IMPORTANT SAFETY INFORMATION (Cont'd)
WARNINGS AND PRECAUTIONS (Cont'd)
Serious Infections (cont'd)

Tuberculosis (cont'd)

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.

Coverage, Coding, and Reimbursement (cont'd)

Claim submission follows strict rules, the impacts below highlight specific considerations by site of care and form type.

Drug Reimbursement Modifiers[8-10]

Modifier Code	Notes	Implications	Form Type	Section	SOC
JW	Drug amount discarded/ not administered to any patient	Without one of these on the form there is autorejection	1500 1450	24D on 1500 44 on 1450	Clinical and facility (hospital)
JZ	Zero drug amount discarded/ not administered to any patient	Without one of these on the form there is autorejection	1500 1450	24D on 1500 44 on 1450	Clinical and facility (hospital)
TB	Informational only, used to inform 340b drug pricing for IRA exclusion of CPI-U penalty	Notice to CMS, only select 340b facilities that are able to use/ required to use	1450	44	Select 340b (short list to be refreshed as needed/HRSA)
JG	Informational only, historically used to inform payment reduction (unnecessary and sunset in 2025)	Avoid reduction of 340b payment	1450	44	Select 340b

Administration Reimbursement Modifiers[11,12]

Modifier Code	Notes	Implications	Form Type	Section	SOC
96365	Simple infusion	Reduction in infusion fees	1500 1450	24D on 1500 44 on 1450	Clinical and facility (hospital)
96413	Complex infusion, MACs scrutinizing use, need to support with notes in medical record	Greater infusion fees	1500 1450	24D on 1500 44 on 1450	Clinical and facility (hospital)

CMS=Centers for Medicare & Medicaid Services; CPI-U=Consumer Price Index for All Urban Consumers; HRSA=Health Resources and Services Administration; IRA=Inflation Reduction Act; MAC=Medicare Administrative Contractors.

IMPORTANT SAFETY INFORMATION (Cont'd)

WARNINGS AND PRECAUTIONS (Cont'd)

Serious Infections (cont'd)

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.

Coverage, Coding, and Reimbursement (cont'd)

Use of JZ Modifier for Zero Drug/Biosimilar Amount Discarded[8]

- The JZ modifier is available for use as of **January 1, 2024**
- Starting **January 1, 2023**, healthcare providers (HCPs) are required to report the JZ modifier on all claims that bill for drugs from single-dose containers that are separately payable under Medicare Part B when there are no discarded amounts

JZ Modifier Example:

Use is applicable for both CMS-1500 (clinic) and CMS-1450 (HOPD) settings.

- A provider treats a 75-kg patient by infusing a 200 mg and 400 mg vial of TOFIDENCE with no waste **(1 mg of TOFIDENCE = 1 unit)**
- There are no discarded amounts, so the provider must use the JZ modifier. (Vial overfill is not reported with the JZ modifier.)
- The provider files a claim with one line for the drug. The claim line should include Q5133 followed by the JZ modifier (attesting that there were no discarded amounts), and the number of units (600 mg) administered in the units field

K. L. D. PROCEDURES, SERVICES, OR SUPPLIES (Explain Unusual Circumstances) CPT/HCPCS	MODIFIER	E. DIAGNOSIS POINTER	F. $ CHARGES	G. DAYS OR UNITS
Q5133	JZ			600

Use of JW Modifier for Drug/Biosimilar Amount Discarded or Not Administered[8]

- Healthcare providers are required to report the JW modifier on Part B drug claims to indicate the amount of discarded product
- The discarded amount is defined as what remains from a single-use vial or other single-use packaging after administering a dose or quantity of drug to a Medicare patient

JW Modifier Example:

The following is for sites other than hospital outpatient departments that use the CMS-1500 form:

- A provider treats a 72-kg patient by infusing 576 mg from a 200 mg and 400 mg vial
- The provider lists the product on 2 lines of the claim; both lines start with Q5133
- The first line represents the 576 mg that were administered to the patient
- The second line represents the 24 mg that were discarded, so those 24 units are recorded and "JW" is added to Q5133. This is known as the JW modifier

K. L. D. PROCEDURES, SERVICES, OR SUPPLIES (Explain Unusual Circumstances) CPT/HCPCS	MODIFIER	E. DIAGNOSIS POINTER	F. $ CHARGES	G. DAYS OR UNITS
Q5133				576
Q5133	JW			24

IMPORTANT SAFETY INFORMATION (Cont'd)

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.

Coverage, Coding, and Reimbursement (cont'd)

NDC Codes for TOFIDENCE[1]

Coding System	Code	Description
NDC	10-digit code: 64406-024-01 11-digit code: 64406-0024-01*	80 mg (4 mL) single-use vial
	10-digit code: 64406-022-01 11-digit code: 64406-0022-01*	200 mg (10 mL) single-use vial
	10-digit code: 64406-023-01 11-digit code: 64406-0023-01*	400 mg (20 mL) single-use vial

*Please note that although the FDA uses a 10-digit format when registering NDCs, payers often require an 11-digit NDC format on claim forms for billing purposes. The 10-digit TOFIDENCE format is converted to an 11-digit code by adding a zero (0) in front of the second group of numbers, eg, 64406-0024-01. It is important to communicate with your payers to determine the appropriate NDC format requirements.

Administration Codes for TOFIDENCE[11]

Type	Code	Description
CPT	96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
	96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug

All coding and documentation requirements should be confirmed with each payer before submitting a claim for reimbursement.

CPT=Current Procedural Terminology; NDC=National Drug Code.

IMPORTANT SAFETY INFORMATION (Cont'd)

WARNINGS AND PRECAUTIONS (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.

Please see Important Safety Information on pages 17-20 and full Prescribing Information, including Boxed Warning.

Sample CMS-1500 Claim Form

Physician Office Setting

Field 17b: Indicate the appropriate National Provider Identifier (NPI).

Field 21: Indicate the most medically appropriate diagnosis code.

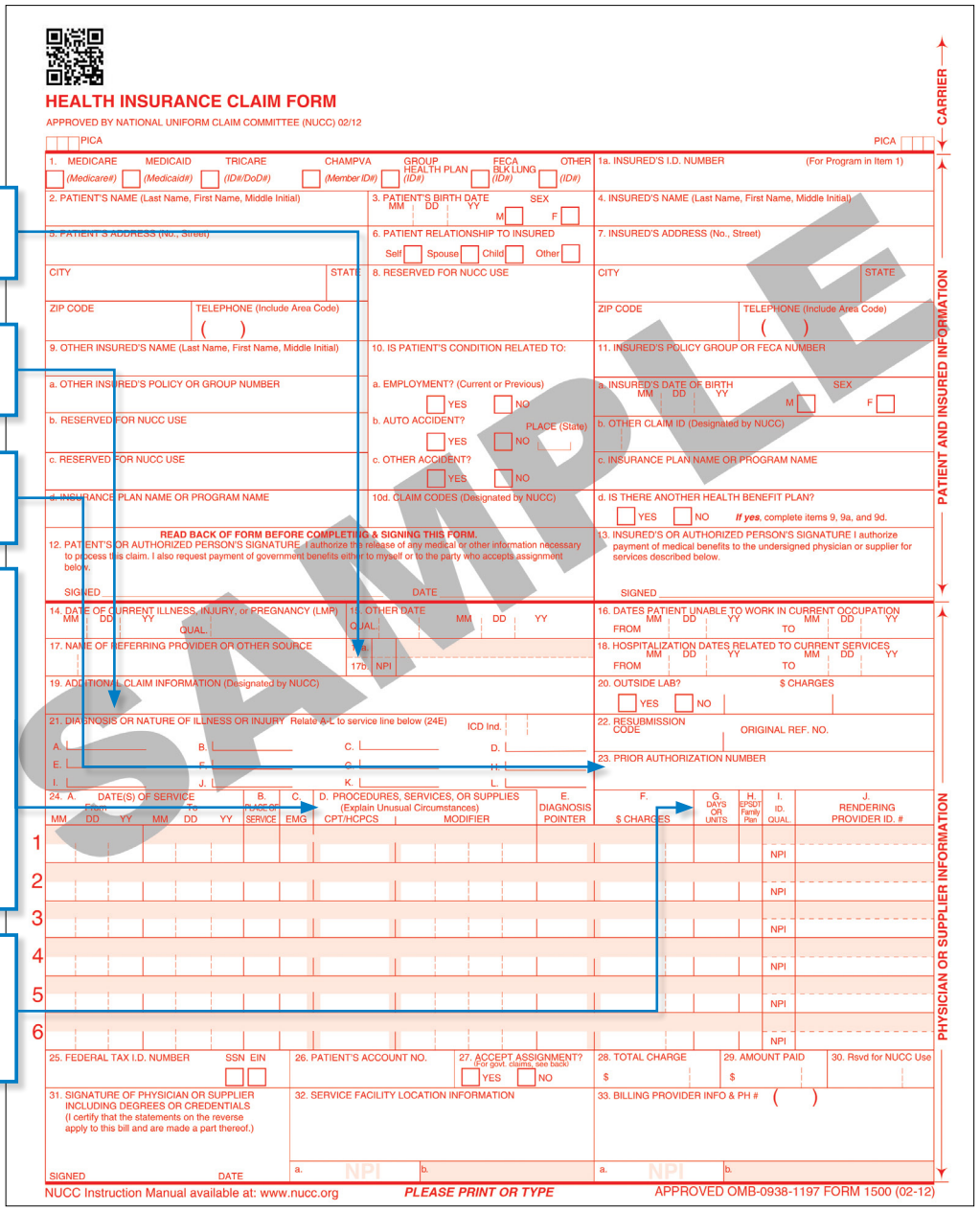
Field 23: If required, report PA number here.

Field 24D:

1. Indicate the appropriate HCPCS code (Q5133).
2. Indicate the appropriate CPT code (96365 or 96413) to report drug administration procedures.
3. Record JZ in the modifier column to indicate that no amount of product was discarded.

Field 24G: Indicate the appropriate HCPCS and/or CPT code units.

*One billable unit of TOFIDENCE is equivalent to 1 mg.



HEALTH INSURANCE CLAIM FORM

APPROVED BY NATIONAL UNIFORM CLAIM COMMITTEE (NUCC) 02/12

PICA

1. MEDICARE (Medicare#) MEDICAID (Medicaid#) TRICARE (ID#/DoD#) CHAMPVA (Member ID#) GROUP HEALTH PLAN (ID#) FECA BLK LUNG (ID#) OTHER (ID#)

1a. INSURED'S I.D. NUMBER (For Program in Item 1)

2. PATIENT'S NAME (Last Name, First Name, Middle Initial)

3. PATIENT'S BIRTH DATE MM DD YY SEX M F

4. INSURED'S NAME (Last Name, First Name, Middle Initial)

5. PATIENT'S ADDRESS (No., Street)

6. PATIENT RELATIONSHIP TO INSURED Self Spouse Child Other

7. INSURED'S ADDRESS (No., Street)

CITY STATE

8. RESERVED FOR NUCC USE

CITY STATE

ZIP CODE TELEPHONE (Include Area Code) ( )

ZIP CODE TELEPHONE (Include Area Code) ( )

9. OTHER INSURED'S NAME (Last Name, First Name, Middle Initial)

10. IS PATIENT'S CONDITION RELATED TO:

11. INSURED'S POLICY GROUP OR FECA NUMBER

a. OTHER INSURED'S POLICY OR GROUP NUMBER

a. EMPLOYMENT? (Current or Previous) YES NO

a. INSURED'S DATE OF BIRTH MM DD YY SEX M F

b. RESERVED FOR NUCC USE

b. AUTO ACCIDENT? PLACE (State) YES NO

b. OTHER CLAIM ID (Designated by NUCC)

c. RESERVED FOR NUCC USE

c. OTHER ACCIDENT? YES NO

c. INSURANCE PLAN NAME OR PROGRAM NAME

d. INSURANCE PLAN NAME OR PROGRAM NAME

10d. CLAIM CODES (Designated by NUCC)

d. IS THERE ANOTHER HEALTH BENEFIT PLAN? YES NO If yes, complete items 9, 9a, and 9d.

READ BACK OF FORM BEFORE COMPLETING & SIGNING THIS FORM.

12. PATIENT'S OR AUTHORIZED PERSON'S SIGNATURE I authorize the release of any medical or other information necessary to process this claim. I also request payment of government benefits either to myself or to the party who accepts assignment below.

SIGNED DATE

13. INSURED'S OR AUTHORIZED PERSON'S SIGNATURE I authorize payment of medical benefits to the undersigned physician or supplier for services described below.

SIGNED

14. DATE OF CURRENT ILLNESS, INJURY, or PREGNANCY (LMP) MM DD YY QUAL.

15. OTHER DATE MM DD YY QUAL.

16. DATES PATIENT UNABLE TO WORK IN CURRENT OCCUPATION MM DD YY FROM MM DD YY TO

17. NAME OF REFERRING PROVIDER OR OTHER SOURCE

17a.

17b. NPI

18. HOSPITALIZATION DATES RELATED TO CURRENT SERVICES MM DD YY FROM MM DD YY TO

19. ADDITIONAL CLAIM INFORMATION (Designated by NUCC)

20. OUTSIDE LAB? YES NO $ CHARGES

21. DIAGNOSIS OR NATURE OF ILLNESS OR INJURY Relate A-L to service line below (24E) ICD Ind.

A. B. C. D. E. F. G. H. I. J. K. L.

22. RESUBMISSION CODE ORIGINAL REF. NO.

23. PRIOR AUTHORIZATION NUMBER

24. A. DATE(S) OF SERVICE From MM DD YY To MM DD YY	B. PLACE OF SERVICE	C. EMG	D. PROCEDURES, SERVICES, OR SUPPLIES (Explain Unusual Circumstances) CPT/HCPCS	MODIFIER	E. DIAGNOSIS POINTER	F. $ CHARGES	G. DAYS OR UNITS	H. EPSDT Family Plan	I. ID. QUAL.	J. RENDERING PROVIDER ID. #
1									NPI	
2									NPI	
3									NPI	
4									NPI	
5									NPI	
6									NPI	

25. FEDERAL TAX I.D. NUMBER SSN EIN

26. PATIENT'S ACCOUNT NO.

27. ACCEPT ASSIGNMENT? (For govt. claims, see back) YES NO

28. TOTAL CHARGE $

29. AMOUNT PAID $

30. Rsvd for NUCC Use

31. SIGNATURE OF PHYSICIAN OR SUPPLIER INCLUDING DEGREES OR CREDENTIALS (I certify that the statements on the reverse apply to this bill and are made a part thereof.)

SIGNED DATE

32. SERVICE FACILITY LOCATION INFORMATION

a. NPI b.

33. BILLING PROVIDER INFO & PH # ( )

a. NPI b.

NUCC Instruction Manual available at: www.nucc.org PLEASE PRINT OR TYPE APPROVED OMB-0938-1197 FORM 1500 (02-12)

CARRIER

PATIENT AND INSURED INFORMATION

PHYSICIAN OR SUPPLIER INFORMATION

SAMPLE

IMPORTANT SAFETY INFORMATION (Cont'd)

WARNINGS AND PRECAUTIONS (Cont'd)

Hepatotoxicity (cont'd)

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.

Ordering Process

TOFIDENCE Product Information

How supplied and packaged[1]	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.	
Carton dimension	**Assembled: 58 mm (L) X 62 mm (W) X 80 mm (H)**	
WAC*	TOFIDENCE (tocilizumab-bavi) 80 mg/4 mL (20 mg/mL) single-dose vial – NDC 64406-024-01	$444
	TOFIDENCE (tocilizumab-bavi) 200 mg/10 mL (20 mg/mL) single-dose vial – NDC 64406-022-01	$1,110
	TOFIDENCE (tocilizumab-bavi) 400 mg/20 mL (20 mg/mL) single-dose vial – NDC 64406-023-01	$2,220
Storage and Handling[1]	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.	

Not actual size.

*Price effective **May 1, 2024**.

IMPORTANT SAFETY INFORMATION (Cont'd)

WARNINGS AND PRECAUTIONS (Cont'd)

Hepatotoxicity (cont'd)

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.

Please see Important Safety Information on pages 17-20 and full Prescribing Information, including Boxed Warning.

Ordering Process (cont'd)

TOFIDENCE can be acquired in 1 of 2 ways:

Buy-and-bill through select specialty distributors

Specialty Distributor*	Phone Number	Fax Number	Website
McKesson Plasma and Biologics	877-625-2566	888-752-7626	https://connect.mckesson.com
McKesson Specialty Care Distribution	855-477-9800	855-824-9489	https://mscs.mckesson.com/
CuraScriptSD	877-599-7748	800-862-6208	www.curascriptsd.com
Besse Medical	800-543-2111	800-543-8695	https://www.besse.com/contact-us
Oncology Supply	800-633-7555	800-248-8205	https://www.oncologysupply.com/contact-us
ASD Healthcare	800-746-6273	800-547-9413	https://www.asdhealthcare.com/contact-us
Cardinal Health SPD	855-855-0708	N/A	Orderexpress.cardinalhealth.com Specialtyonline.cardinalhealth.com
Metro Medical	800-768-2002 615-329-2002	N/A	metromedicalorder.com

TOFIDENCE is accessible via an open specialty pharmacy network.

*Specialty distributor and contact information are current as of **January 1, 2024**, and are subject to change.

IMPORTANT SAFETY INFORMATION (Cont'd)

WARNINGS AND PRECAUTIONS (Cont'd)

Hepatotoxicity (cont'd)

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.

Please see Important Safety Information on pages 17-20 and full Prescribing Information, including Boxed Warning.

Ordering Requirements by Type of Coverage

Payer Reimbursement for Drugs and Services

If your patient is covered by:

Medicare Part B

For biosimilars, Medicare Part B reimburses physician services, including drug administration services, based on the Medicare Physician Fee Schedule (MPFS) at ASP plus 8% of the reference product, as published quarterly by CMS.[3]* If the ASP is not available, then the biosimilar will be reimbursed at the WAC plus 3%.[4] Medicare Part B pays for 80% of the allowed charges for TOFIDENCE and its administration, with the beneficiary responsible for the remaining 20% coinsurance. Medicare Part B patients could have a secondary, or supplemental, plan (eg, Medigap) to help cover the Part B 20% coinsurance.[13]

Medicaid and Private Payers

Some payers may require PA for TOFIDENCE, or they may have other requirements.

Medicaid: Reimbursement for TOFIDENCE and its administration services varies by state. Medicaid rates are updated quarterly and can be found on the Medicaid.gov website.

Private Payers: Reimbursement for TOFIDENCE and its administration services will vary by payer, depending on the specific provisions outlined in a healthcare provider's contract.

Medicare, commercial (private) payers, and Medicaid each have different reimbursement policies. Being familiar with these differences may help to minimize potential challenges when seeking reimbursement.

*Medicare Part B reimbursement is subject to sequestration, which reduces the portion of the payment paid by Medicare by 2%. As a result, the payment rate is effectively ASP + 4.3%.[11] If the ASP is not available, then the biosimilar will be reimbursed at the WAC plus 3%.[4]

IMPORTANT SAFETY INFORMATION (Cont'd)
WARNINGS AND PRECAUTIONS (Cont'd)
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.

Please see Important Safety Information on pages 17-20 and full Prescribing Information, including Boxed Warning.

Ordering Considerations

To help ensure a site of care's chosen distributor or pharmacy has enough inventory of the drug to meet the site of care's anticipated needs, the site may wish to review the following information:

- **Weekly** purchase amount (units)
- Weekly **purchase amount by contract**—Wholesale Acquisition Cost, Group Purchasing Organization, 340B
- Anticipated **TOFIDENCE** adoption
- Anticipated date for **large orders**

IMPORTANT SAFETY INFORMATION (Cont'd)
WARNINGS AND PRECAUTIONS (Cont'd)
Changes in Laboratory Parameters (cont'd)

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 page 18.)

Please see Important Safety Information on pages 17-20 and full Prescribing Information, including Boxed Warning.

Patient Services Overview:
Biogen Biosimilar Support Services

Help support your patients with financial and insurance assistance

Benefits investigation and PA support

Biogen Biosimilar Support Services can help patients determine coverage options for TOFIDENCE.

Patient financial assistance

Biogen Biosimilar Support Services aims to support patients regardless of insurance coverage.

To learn more information or to enroll your patient in Biogen Biosimilar Support Services, please visit https://biogenbiosimilarsupportservices-tofidence.com.

For more information about these services, contact Biogen Biosimilar Support Services at 1-877-422-8360, Monday through Friday, 8:30 AM – 8 PM ET.

IMPORTANT SAFETY INFORMATION (Cont'd)
WARNINGS AND PRECAUTIONS (Cont'd)
Changes in Laboratory Parameters (cont'd)

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.

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.

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 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.

IMPORTANT SAFETY INFORMATION (Cont'd)

WARNINGS AND PRECAUTIONS (Cont'd)

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. 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%).

IMPORTANT SAFETY INFORMATION (Cont'd)

WARNINGS AND PRECAUTIONS (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.

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.

Tofidence™
tocilizumab-bavi

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Please see Important Safety Information on page 17-20 and full Prescribing Information, including Boxed Warning.

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