HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AVSOLA™ safely and effectively. See full prescribing information for AVSOLA.

AVSOLA (infliximab-axxq) for injection, for intravenous use
Initial U.S. Approval: 2019
AVSOLA (infliximab-axxq) is biosimilar* to REMICADE (infliximab).

WARNING: SERIOUS INFECTIONS and MALIGNANCY
See full prescribing information for complete boxed warning.

- Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis) and infections due to other opportunistic pathogens.
- Discontinue AVSOLA if a patient develops a serious infection.
- Perform test for latent TB; if positive, start treatment for TB prior to starting AVSOLA. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)
- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, including infliximab products.
- Postmarketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF-blockers including infliximab products. Almost all had received azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of cases were reported in patients with Crohn's disease or ulcerative colitis, most of whom were adolescent or young adult males. (5.2)

---------------------------INDICATIONS AND USAGE---------------------------
AVSOLA is a tumor necrosis factor (TNF) blocker indicated for:
Crohn's Disease:
- reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. (1.1)
- reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease. (1.1)

Pediatric Crohn's Disease: reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy. (1.2)
Ulcerative Colitis: reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. (1.3)
Pediatric Ulcerative Colitis: reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy. (1.4)
Rheumatoid Arthritis in combination with methotrexate: reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease. (1.5)
Ankylosing Spondylitis: reducing signs and symptoms in patients with active disease. (1.6)
Psoriatic Arthritis: reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function. (1.7)
Plaque Psoriasis: treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. (1.8)

-----------------------DOSAGE AND ADMINISTRATION----------------------
AVSOLA is administered by intravenous infusion over a period of not less than 2 hours.
Crohn's Disease: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response. (2.1)
Pediatric Crohn's Disease: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. (2.2)
Ulcerative Colitis: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. (2.3)
Pediatric Ulcerative Colitis: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. (2.4)
Rheumatoid Arthritis: In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks. (2.5)
Ankylosing Spondylitis: 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks. (2.6)

Psoriatic Arthritis and *Plaque Psoriasis*: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. (2.7) and (2.8)

---------------------DOSAGE FORMS AND STRENGTHS--------------------
For injection: 100 mg of lyophilized infliximab-axxq in a 20 mL single-dose vial for intravenous infusion. (3)

------------------------------CONTRAINDICATIONS-----------------------------
- AVSOLA doses >5 mg/kg in moderate to severe heart failure. (4)
- Previous severe hypersensitivity reaction to infliximab products or known hypersensitivity to inactive components of AVSOLA or to any murine proteins. (4)

-----------------------WARNINGS AND PRECAUTIONS-----------------------
- *Serious infections* – do not give AVSOLA during an active infection. If an infection develops, monitor carefully and stop AVSOLA if infection becomes serious. (5.1)
- *Invasive fungal infections* – for patients who develop a systemic illness on AVSOLA, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic. (5.1)
- *Malignancies* – the incidence of malignancies, including invasive cervical cancer and lymphoma, was greater in infliximab-treated patients than in controls. Due to the risk of HSTCL carefully assess the risk/benefit especially if the patient has Crohn's disease or ulcerative colitis, is male, and is receiving azathioprine or 6-mercaptopurine treatment. (5.2)
- *Hepatitis B virus reactivation* – test for HBV infection before starting AVSOLA. Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop AVSOLA and begin anti-viral therapy. (5.3)
- *Hepatotoxicity* – severe hepatic reactions, some fatal or necessitating liver transplantation. Stop AVSOLA in cases of jaundice and/or marked liver enzyme elevations. (5.4)
- *Heart failure* – new onset or worsening symptoms may occur. (4, 5.5)
- *Cytopenias* – advise patients to seek immediate medical attention if signs and symptoms develop, and consider stopping AVSOLA. (5.6)
- *Hypersensitivity* – serious infusion reactions including anaphylaxis or serum sickness-like reactions may occur. (5.7)
- *Cardiovascular and Cerebrovascular Reactions* – Cerebrovascular accidents, myocardial infarctions (some fatal), and arrhythmias have been reported during and within 24 hours of initiation of infliximab product infusion. Monitor patients during AVSOLA infusion and if serious reaction occurs, discontinue infusion. (5.8)
- *Demyelinating disease* – exacerbation or new onset may occur. (5.9)
- *Lupus-like syndrome* – stop AVSOLA if syndrome develops. (5.14)
- *Live vaccines or therapeutic infectious agents* – should not be given with AVSOLA. Bring pediatric patients up to date with all vaccinations prior to initiating AVSOLA. At least a six-month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab products. (5.15)

------------------------------ADVERSE REACTIONS------------------------------
Most common adverse reactions (>10%) – infections (e.g., upper respiratory, sinusitis, and pharyngitis), infusion-related reactions, headache, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch***.**

-------------------------------DRUG INTERACTIONS------------------------------
Use with anakinra or abatacept – increased risk of serious infections. (7.1)

-----------------------USE IN SPECIFIC POPULATIONS---------------------
Pediatric Use – Infliximab products have not been studied in children with Crohn's disease or ulcerative colitis <6 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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

Revised: 12/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION
WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

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

AVSOLA should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before AVSOLA use and during therapy.[1,2] Treatment for latent infection should be initiated prior to AVSOLA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with AVSOLA 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 AVSOLA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF-blockers, including infliximab products *[see Warnings and Precautions (5.2)].*

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF-blockers including infliximab products. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males.

1 INDICATIONS AND USAGE

1.1 Crohn's Disease

AVSOLA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

AVSOLA is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.

1.2 Pediatric Crohn's Disease

AVSOLA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

1.3 Ulcerative Colitis

AVSOLA is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

1.4 Pediatric Ulcerative Colitis

AVSOLA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

1.5 Rheumatoid Arthritis

AVSOLA, in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.

1.6 Ankylosing Spondylitis

AVSOLA is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

1.7 Psoriatic Arthritis

AVSOLA is indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

1.8 Plaque Psoriasis

AVSOLA is indicated for the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. AVSOLA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning, Warnings and Precautions (5)]*.

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2   DOSAGE AND ADMINISTRATION

2.1   Crohn's Disease

The recommended dose of AVSOLA is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of adults with moderately to severely active Crohn's disease or fistulizing Crohn's disease. For adult patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. Patients who do not respond by Week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue AVSOLA in these patients.

2.2   Pediatric Crohn's Disease

The recommended dose of AVSOLA for pediatric patients 6 years and older with moderately to severely active Crohn's disease is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks.

2.3   Ulcerative Colitis

The recommended dose of AVSOLA is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of adult patients with moderately to severely active ulcerative colitis.

2.4   Pediatric Ulcerative Colitis

The recommended dose of AVSOLA for pediatric patients 6 years and older with moderately to severely active ulcerative colitis is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks.

2.5   Rheumatoid Arthritis

The recommended dose of AVSOLA is 3 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active rheumatoid arthritis. AVSOLA should be given in combination with methotrexate. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at higher doses *[see Adverse Reactions (6.1)]*.

2.6   Ankylosing Spondylitis

The recommended dose of AVSOLA is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks thereafter for the treatment of active ankylosing spondylitis.

2.7   Psoriatic Arthritis

The recommended dose of AVSOLA is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of psoriatic arthritis. AVSOLA can be used with or without methotrexate.

2.8 Plaque Psoriasis

The recommended dose of AVSOLA is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of chronic severe (i.e., extensive and/or disabling) plaque psoriasis.

2.9 Monitoring to Assess Safety

Prior to initiating AVSOLA and periodically during therapy, patients should be evaluated for active tuberculosis and tested for latent infection *[see Warnings and Precautions (5.1)]*.

2.10 Administration Instructions Regarding Infusion Reactions

Adverse effects during administration of infliximab products have included flu-like symptoms, headache, dyspnea, hypotension, transient fever, chills, gastrointestinal symptoms, and skin rashes. Anaphylaxis might occur at any time during AVSOLA infusion. Approximately 20% of patients in all clinical trials of infliximab experienced an infusion reaction compared with 10% of placebo-treated patients *[see Adverse Reactions (6.1)]*. Prior to infusion with AVSOLA, premedication may be administered at the physician's discretion. Premedication could include antihistamines (anti-H1 +/- anti-H2), acetaminophen and/or corticosteroids.

During infusion, mild to moderate infusion reactions may improve following slowing or suspension of the infusion, and upon resolution of the reaction, reinitiation at a lower infusion rate and/or therapeutic administration of antihistamines, acetaminophen, and/or corticosteroids. For patients that do not tolerate the infusion following these interventions, AVSOLA should be discontinued.

During or following infusion, patients who have severe infusion-related hypersensitivity reactions should be discontinued from further AVSOLA treatment. The management of severe infusion reactions should be dictated by the signs and symptoms of the reaction. Appropriate personnel and medication should be available to treat anaphylaxis if it occurs.

2.11 General Considerations and Instructions for Preparation and Administration

AVSOLA is intended for use under the guidance and supervision of a physician. The reconstituted infusion solution should be prepared by a trained medical professional using aseptic technique by the following procedure:

1. Calculate the dose, total volume of reconstituted AVSOLA solution required and the number of AVSOLA vials needed. Each AVSOLA vial contains 100 mg of the infliximab-axxq antibody.
2. Reconstitute each AVSOLA vial with 10 mL of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle as follows: Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab-axxq is a protein. Do not use if the lyophilized cake has not fully dissolved or if opaque particles, discoloration, or other foreign particles are present.
3. Dilute the total volume of the reconstituted AVSOLA solution dose to 250 mL with sterile 0.9% Sodium Chloride Injection, USP, by withdrawing a volume equal to the volume of reconstituted AVSOLA from

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the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag. Do not dilute the reconstituted AVSOLA solution with any other diluent. Slowly add the total volume of reconstituted AVSOLA solution to the 250 mL infusion bottle or bag. Gently mix. The resulting infusion concentration should range between 0.4 mg/mL and 4 mg/mL.

4. The AVSOLA infusion should begin within 3 hours of reconstitution and dilution. The infusion must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less). The vials do not contain antibacterial preservatives. Therefore, any unused portion of the infusion solution should not be stored for reuse.

5. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of AVSOLA with other agents. AVSOLA should not be infused concomitantly in the same intravenous line with other agents.

6. Parenteral drug products should be inspected visually before and after reconstitution for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.

3   DOSAGE FORMS AND STRENGTHS

For injection: 100 mg of infliximab-axxq as a white to slightly yellow lyophilized powder in a single-dose vial, for intravenous use.

4   CONTRAINDICATIONS

AVSOLA at doses >5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating infliximab in patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), infliximab treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*.

AVSOLA should not be re-administered to patients who have experienced a severe hypersensitivity reaction to infliximab products. Additionally, AVSOLA should not be administered to patients with known hypersensitivity to inactive components of the product or to any murine proteins.

5   WARNINGS AND PRECAUTIONS

5.1   Serious Infections

Patients treated with infliximab products are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, salmonellosis and tuberculosis have been reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease.

Treatment with AVSOLA should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at

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greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

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

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving infliximab products, including patients who have previously received treatment for latent or active tuberculosis. Cases of active tuberculosis have also occurred in patients being treated with infliximab products during treatment for latent tuberculosis.

Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating AVSOLA and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF-blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating AVSOLA, even for patients previously vaccinated with Bacille Calmette-Guérin (BCG).

Anti-tuberculosis therapy should also be considered prior to initiation of AVSOLA 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.

Tuberculosis should be strongly considered in patients who develop a new infection during AVSOLA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with AVSOLA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with AVSOLA.

AVSOLA should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with AVSOLA should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

Invasive Fungal Infections

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis

may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

5.2   Malignancies

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤18 years of age), including infliximab products. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF-blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported postmarketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports.

Lymphomas

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF-blocker compared with control patients. In the controlled and open-label portions of infliximab clinical trials, 5 patients developed lymphomas among 5707 patients treated with infliximab (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population. Patients with Crohn's disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Hepatosplenic T-cell Lymphoma (HSTCL)

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF-blockers including infliximab products. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males. It is uncertain whether the occurrence of HSTCL is related to TNF-blockers or TNF-blockers in combination with these other immunosuppressants. When treating patients, consideration of whether to use AVSOLA alone or in combination with other immunosuppressants such as azathioprine or 6-mercaptopurine should take into account a possibility that there is a higher risk of HSTCL with combination therapy versus an observed increased risk of immunogenicity and hypersensitivity reactions with infliximab product monotherapy from the clinical trial data from studies with infliximab *[see Warnings and Precautions (5.7) and Adverse Reactions (6.1)]*.

Skin Cancer

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocker therapy, including infliximab products *[see Adverse Reactions (6.2)]*. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Cervical Cancer

A population-based retrospective cohort study using data from Swedish national health registries found a 2- to 3-fold increase in the incidence of invasive cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, particularly those over 60 years of age. A causal relationship between infliximab products and cervical cancer cannot be excluded. Periodic screening should continue in women treated with AVSOLA *[see Adverse Reactions (6.2)]*.

Other Malignancies

In the controlled portions of clinical trials of some TNF-blocking agents including infliximab products, more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been observed in patients receiving those TNF-blockers compared with control patients. During the controlled portions of trials with infliximab, in patients with moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 14 patients were diagnosed with malignancies (excluding lymphoma and NMSC) among 4019 infliximab-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among infliximab-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for infliximab-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among infliximab-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.

In a clinical trial exploring the use of infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking *[see Adverse Reactions (6.1)]*. Prescribers should exercise caution when considering the use of AVSOLA in patients with moderate to severe COPD.

Psoriasis patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for infliximab, NMSCs were more common in patients with previous phototherapy *[see Adverse Reactions (6.1)]*.

The potential role of TNF-blocking therapy in the development of malignancies is not known *[see Adverse Reactions (6.1)]*. Rates in clinical trials for infliximab cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering AVSOLA treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving AVSOLA.

5.3   Hepatitis B Virus Reactivation

Use of TNF-blockers, including infliximab products, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also

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contribute to HBV reactivation. Patients should be tested for HBV infection before initiating TNF-blocker therapy, including AVSOLA. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF-blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF-blockers should be stopped and anti-viral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF-blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF-blocker therapy in this situation and monitor patients closely.

5.4   Hepatotoxicity

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis, have been reported in postmarketing data in patients receiving infliximab products. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between 2 weeks to more than 1 year after initiation of infliximab; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develop, AVSOLA should be discontinued, and a thorough investigation of the abnormality should be undertaken. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving infliximab products without progression to severe hepatic injury *[see Adverse Reactions (6.1)]*.

5.5   Patients with Heart Failure

Infliximab products have been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of infliximab in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg infliximab, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been postmarketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. There have also been postmarketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer AVSOLA to patients with heart failure, they should be closely monitored during therapy, and AVSOLA should be discontinued if new or worsening symptoms of heart failure appear *[see Contraindications (4) and Adverse Reactions (6.1)]*.

5.6   Hematologic Reactions

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving infliximab products. The causal relationship to infliximab product therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with AVSOLA who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on AVSOLA. Discontinuation of AVSOLA therapy should be considered in patients who develop significant hematologic abnormalities.

5.7   Hypersensitivity

Infliximab products have been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include anaphylaxis, urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of infusion.

However, in some cases, serum sickness-like reactions have been observed in patients after initial therapy with infliximab products (i.e., as early as after the second dose), and when therapy with infliximab products was reinstituted following an extended period without treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with a marked increase in antibodies to infliximab products, loss of detectable serum concentrations of infliximab products, and possible loss of drug efficacy.

AVSOLA should be discontinued for severe hypersensitivity reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction *[see Adverse Reactions (6.1)]*.

In rheumatoid arthritis, Crohn's disease and psoriasis clinical trials, re-administration of infliximab after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment *[see Adverse Reactions (6.1)]*. In general, the benefit-risk of re-administration of AVSOLA after a period of no-treatment, especially as a re-induction regimen given at weeks 0, 2 and 6, should be carefully considered. In the case where AVSOLA maintenance therapy for psoriasis is interrupted, AVSOLA should be reinitiated as a single-dose followed by maintenance therapy.

5.8   Cardiovascular and Cerebrovascular Reactions During and After Infusion

Serious cerebrovascular accidents, myocardial ischemia/infarction (some fatal), hypotension, hypertension, and arrhythmias have been reported during and within 24 hours of initiation of infliximab product infusion. Cases of transient visual loss have been reported during or within 2 hours of infusion of infliximab products. Monitor patients during infusion and if serious reaction occurs, discontinue infusion. Further management of reactions should be dictated by signs and symptoms *[see Adverse Reactions (6)]*.

5.9   Neurologic Reactions

Agents that inhibit TNF have been associated with CNS manifestation of systemic vasculitis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of AVSOLA in patients with these neurologic disorders and should consider discontinuation of AVSOLA if these disorders develop.

5.10   Use with Anakinra

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNFα-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse reactions seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNFα-blocking agents. Therefore, the combination of AVSOLA and anakinra is not recommended.

5.11 Use with Abatacept

In clinical studies, concurrent administration of TNF-blocking agents and abatacept have been associated with an increased risk of infections including serious infections compared with TNF-blocking agents alone, without increased clinical benefit. Therefore, the combination of AVSOLA and abatacept is not recommended *[see Drug Interactions (7.1)]*.

5.12 Concurrent Administration with Other Biological Therapeutics

There is insufficient information regarding the concomitant use of infliximab products with other biological therapeutics used to treat the same conditions as AVSOLA. The concomitant use of AVSOLA with these biologics is not recommended because of the possibility of an increased risk of infection *[see Drug Interactions (7.3)]*.

5.13 Switching Between Biological Disease-Modifying Antirheumatic Drugs (DMARDs)

Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection.

5.14 Autoimmunity

Treatment with infliximab products may result in the formation of autoantibodies and in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with AVSOLA, treatment should be discontinued *[see Adverse Reactions (6.1)]*.

5.15 Live Vaccines/Therapeutic Infectious Agents

In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines can result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with AVSOLA is not recommended.

Fatal outcome due to disseminated BCG infection has been reported in an infant who received a BCG vaccine after *in utero* exposure to infliximab products. Infliximab products are known to cross the placenta and has been detected up to 6 months following birth. At least a six-month waiting period following birth is recommended before the administration of any live vaccine to infants exposed *in utero* to infliximab products. Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with AVSOLA.

It is recommended that all pediatric patients be brought up to date with all vaccinations prior to initiating AVSOLA therapy. The interval between vaccination and initiation of AVSOLA therapy should be in accordance with current vaccination guidelines.

6   ADVERSE REACTIONS

6.1   Clinical Trials Experience

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

Adverse Reactions in Adults

The data described herein reflect exposure to infliximab in 4779 adult patients (1304 patients with rheumatoid arthritis, 1106 patients with Crohn's disease, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 484 with ulcerative colitis, 1373 with plaque psoriasis, and 17 patients with other conditions), including 2625 patients exposed beyond 30 weeks and 374 exposed beyond 1 year. *[For information on adverse reactions in pediatric patients, see Adverse Reactions (6.1)]*. One of the most common reasons for discontinuation of treatment was infusion-related reactions (e.g., dyspnea, flushing, headache and rash).

Infusion-related Reactions

An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion. In Phase 3 clinical studies, 18% of infliximab-treated patients experienced an infusion reaction compared to 5% of placebo-treated patients. Of infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period.

Among all infliximab infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued infliximab treatment because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. Infliximab infusions beyond the initial infusion were not associated with a higher incidence of reactions. The infusion reaction rates remained stable in psoriasis through 1 year in psoriasis Study I. In psoriasis Study II, the rates were variable over time and somewhat higher following the final infusion than after the initial infusion. Across the 3 psoriasis studies, the percent of total infusions resulting in infusion reactions (i.e., an adverse event occurring within 1 hour) was 7% in the 3 mg/kg group, 4% in the 5 mg/kg group, and 1% in the placebo group.

Patients who became positive for antibodies to infliximab were more likely (approximately two- to three-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of both antibodies to infliximab and infusion reactions *[see Adverse Reactions (6.1) and Drug Interactions (7.4)]*.

Infusion Reactions Following Re-administration

In a clinical trial of patients with moderate to severe psoriasis designed to assess the efficacy of long-term maintenance therapy versus re-treatment with an induction regimen of infliximab following disease flare, 4% (8/219) of patients in the re-treatment therapy arm experienced serious infusion reactions versus <1% (1/222) in the maintenance therapy arm. Patients enrolled in this trial did not receive any concomitant immunosuppressant therapy. In this study, the majority of serious infusion reactions occurred during the second infusion at Week 2. Symptoms included, but were not limited to, dyspnea, urticaria, facial edema, and hypotension. In all cases, treatment with infliximab was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed Reactions/Reactions Following Re-administration

In psoriasis studies, approximately 1% of infliximab-treated patients experienced a possible delayed hypersensitivity reaction, generally reported as serum sickness or a combination of arthralgia and/or myalgia with fever and/or rash. These reactions generally occurred within 2 weeks after repeat infusion.

Infections

In infliximab clinical studies, treated infections were reported in 36% of infliximab-treated patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among infliximab-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported postmarketing. Most of these cases of tuberculosis occurred within the first 2 months after initiation of therapy with infliximab and may reflect recrudescence of latent disease *[see Warnings and Precautions (5.1)]*. In the 1 year placebo-controlled studies RA I and RA II, 5.3% of patients receiving infliximab every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients receiving MTX. Of 924 patients receiving infliximab, 1.7% developed pneumonia and 0.4% developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg or 10 mg/kg infliximab infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX, serious infections were more frequent in the 10 mg/kg infliximab group (5.3%) than the 3 mg/kg or placebo groups (1.7% in both). During the 54-week Crohn's II Study, 15% of patients with fistulizing Crohn's disease developed a new fistula-related abscess.

In infliximab clinical studies in patients with ulcerative colitis, infections treated with antimicrobials were reported in 27% of infliximab-treated patients (average of 41 weeks of follow-up) and in 18% of placebo-treated patients (average 32 weeks of follow-up). The types of infections, including serious infections, reported in patients with ulcerative colitis were similar to those reported in other clinical studies.

The onset of serious infections may be preceded by constitutional symptoms such as fever, chills, weight loss, and fatigue. The majority of serious infections, however, may also be preceded by signs or symptoms localized to the site of the infection.

Autoantibodies/Lupus-like Syndrome

Approximately half of the infliximab-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately one-fifth of infliximab-treated patients compared with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

Malignancies

In controlled trials, more infliximab-treated patients developed malignancies than placebo-treated patients *[see Warnings and Precautions (5.2)]*.

In a randomized controlled clinical trial exploring the use of infliximab in patients with moderate to severe COPD who were either current smokers or ex-smokers, 157 patients were treated with infliximab at doses similar to those used in rheumatoid arthritis and Crohn's disease. Of these infliximab-treated patients, 9 developed a malignancy, including 1 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 3.51 - 14.56). There was 1 reported malignancy among 77 control patients for a rate of 1.63 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 0.04 - 9.10). The majority of the malignancies developed in the lung or head and neck.

Patients with Heart Failure

In a randomized study evaluating infliximab in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction ≤35%), 150 patients were randomized to receive treatment with 3 infusions of infliximab 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg infliximab dose. At 1 year, 8 patients in the 10 mg/kg infliximab group had died compared with 4 deaths each in the 5 mg/kg infliximab and the placebo groups. There were trends toward increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg infliximab treatment groups, versus placebo. Infliximab has not been studied in patients with mild heart failure (NYHA Class I/II) *[see Contraindications (4) and Warnings and Precautions (5.5)]*.

Immunogenicity

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

Treatment with infliximab products can be associated with the development of antibodies to infliximab products. An enzyme immunoassay (EIA) method was originally used to measure anti-infliximab antibodies in clinical studies of infliximab. The EIA method is subject to interference by serum infliximab, possibly resulting in an underestimation of the rate of patient antibody formation. A separate, drug-tolerant electrochemiluminescence immunoassay (ECLIA) method for detecting antibodies to infliximab was subsequently developed and validated. This method is 60-fold more sensitive than the original EIA. With the ECLIA method, all clinical samples can be classified as either positive or negative for antibodies to infliximab without the need for the inconclusive category.

The incidence of antibodies to infliximab was based on the original EIA method in all clinical studies of infliximab except for the Phase 3 study in pediatric patients with ulcerative colitis where the incidence of antibodies to infliximab was detected using both the EIA and ECLIA methods *[see Adverse Reactions, Pediatric Ulcerative Colitis (6.1)]*.

The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through 1 to 2 years of treatment with infliximab. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving infliximab after drug-free intervals >16 weeks. In a study of psoriatic arthritis in which 191 patients received 5 mg/kg with or without MTX, antibodies to infliximab occurred in 15% of patients. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction *[see Adverse Reactions (6.1)]* than were patients who were antibody negative. Antibody development was lower among

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rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX.

In the psoriasis Study II, which included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 36% of patients treated with 5 mg/kg every 8 weeks for 1 year, and in 51% of patients treated with 3 mg/kg every 8 weeks for 1 year. In the psoriasis Study III, which also included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 20% of patients treated with 5 mg/kg induction (weeks 0, 2 and 6), and in 27% of patients treated with 3 mg/kg induction. Despite the increase in antibody formation, the infusion reaction rates in Studies I and II in patients treated with 5 mg/kg induction followed by every 8-week maintenance for 1 year and in Study III in patients treated with 5 mg/kg induction (14.1%-23.0%) and serious infusion reaction rates (<1%) were similar to those observed in other study populations. The clinical significance of apparent increased immunogenicity on efficacy and infusion reactions in psoriasis patients as compared to patients with other diseases treated with infliximab products over the long-term is not known.

Hepatotoxicity

Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported in patients receiving infliximab products *[see Warnings and Precautions (5.4)]*. Reactivation of hepatitis B virus has occurred in patients receiving TNF-blocking agents, including infliximab products, who are chronic carriers of this virus *[see Warnings and Precautions (5.3)]*.

In clinical trials in rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving infliximab than in controls (Table 1), both when infliximab was given as monotherapy and when it was used in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of infliximab, or modification of concomitant medications.

Table 1: Proportion of patients with elevated ALT in clinical trials

	Proportion of patients with elevated ALT					
	>1 to <3 × ULN		≥3 × ULN		≥5 × ULN	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
Rheumatoid arthritis[a]	24%	34%	3%	4%	<1%	<1%
Crohn's disease[b]	34%	39%	4%	5%	0%	2%
Ulcerative colitis[c]	12%	17%	1%	2%	<1%	<1%
Ankylosing spondylitis[d]	15%	51%	0%	10%	0%	4%
Psoriatic arthritis[e]	16%	50%	0%	7%	0%	2%
Plaque psoriasis[f]	24%	49%	<1%	8%	0%	3%

[a] Placebo patients received methotrexate while patients treated with infliximab received both infliximab and methotrexate. Median follow-up was 58 weeks.

[b] Placebo patients in the 2 Phase 3 trials in Crohn's disease received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in ALT analysis. Median follow-up was 54 weeks.

[c] Median follow-up was 30 weeks. Specifically, the median duration of follow-up was 30 weeks for placebo and 31 weeks for infliximab.

[d] Median follow-up was 24 weeks for the placebo group and 102 weeks for the infliximab group.

[e] Median follow-up was 39 weeks for the infliximab group and 18 weeks for the placebo group.

ALT values are obtained in 2 Phase 3 psoriasis studies with median follow-up of 50 weeks for infliximab and 16 weeks for placebo.

Adverse Reactions in Psoriasis Studies

During the placebo-controlled portion across the 3 clinical trials up to Week 16, the proportion of patients who experienced at least 1 serious adverse reaction (SAE; defined as resulting in death, life threatening, requires hospitalization, or persistent or significant disability/incapacity) was 0.5% in the 3 mg/kg infliximab group, 1.9% in the placebo group, and 1.6% in the 5 mg/kg infliximab group.

Among patients in the 2 Phase 3 studies, 12.4% of patients receiving infliximab 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 SAE in Study I. In Study II, 4.1% and 4.7% of patients receiving infliximab 3 mg/kg and 5 mg/kg every 8 weeks, respectively, through 1 year of maintenance treatment experienced at least 1 SAE.

One death due to bacterial sepsis occurred 25 days after the second infusion of 5 mg/kg infliximab. Serious infections included sepsis, and abscesses. In Study I, 2.7% of patients receiving infliximab 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 serious infection. In Study II, 1.0% and 1.3% of patients receiving infliximab 3 mg/kg and 5 mg/kg, respectively, through 1 year of treatment experienced at least 1 serious infection. The most common serious infection (requiring hospitalization) was abscess (skin, throat, and peri-rectal) reported by 5 (0.7%) patients in the 5 mg/kg infliximab group. Two active cases of tuberculosis were reported: 6 weeks and 34 weeks after starting infliximab.

In the placebo-controlled portion of the psoriasis studies, 7 of 1123 patients who received infliximab at any dose were diagnosed with at least one NMSC compared to 0 of 334 patients who received placebo.

In the psoriasis studies, 1% (15/1373) of patients experienced serum sickness or a combination of arthralgia and/or myalgia with fever, and/or rash, usually early in the treatment course. Of these patients, 6 required hospitalization due to fever, severe myalgia, arthralgia, swollen joints, and immobility.

Other Adverse Reactions

Safety data are available from 4779 infliximab-treated adult patients, including 1304 with rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 1373 with plaque psoriasis and 17 with other conditions. *[For information on other adverse reactions in pediatric patients, see Adverse Reactions (6.1)].* Adverse reactions reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are in Table 2. The types and frequencies of adverse reactions observed were similar in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and Crohn's disease patients treated with infliximab except for abdominal pain, which occurred in 26% of patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received infliximab to provide meaningful comparisons.

Table 2: Adverse reactions occurring in 5% or more of patients receiving 4 or more infusions for rheumatoid arthritis

	Placebo	Infliximab
	(n=350)	(n=1129)
Average weeks of follow-up	59	66
Gastrointestinal		
Nausea	20%	21%
Abdominal pain	8%	12%
Diarrhea	12%	12%
Dyspepsia	7%	10%
Respiratory		
Upper respiratory tract infection	25%	32%
Sinusitis	8%	14%
Pharyngitis	8%	12%
Coughing	8%	12%
Bronchitis	9%	10%
Skin and appendages disorders		
Rash	5%	10%
Pruritus	2%	7%
Body as a whole-general disorders		
Fatigue	7%	9%
Pain	7%	8%
Resistance mechanism disorders		
Fever	4%	7%
Moniliasis	3%	5%
Central and peripheral nervous system disorders		
Headache	14%	18%
Musculoskeletal system disorders		
Arthralgia	7%	8%
Urinary system disorders		
Urinary tract infection	6%	8%
Cardiovascular disorders, general		
Hypertension	5%	7%

The most common serious adverse reactions observed in clinical trials were infections *[see Adverse Reactions (6.1)]*. Other serious, medically relevant adverse reactions ≥0.2% or clinically significant adverse reactions by body system were as follows:

- *Body as a whole*: allergic reaction, edema
- *Blood*: pancytopenia
- *Cardiovascular*: hypotension
- *Gastrointestinal*: constipation, intestinal obstruction
- *Central and Peripheral Nervous*: dizziness
- *Heart Rate and Rhythm*: bradycardia
- *Liver and Biliary*: hepatitis
- *Metabolic and Nutritional*: dehydration
- *Platelet, Bleeding and Clotting*: thrombocytopenia
- *Neoplasms*: lymphoma
- *Red Blood Cell*: anemia, hemolytic anemia
- *Resistance Mechanism*: cellulitis, sepsis, serum sickness, sarcoidosis
- *Respiratory*: lower respiratory tract infection (including pneumonia), pleurisy, pulmonary edema
- *Skin and Appendages*: increased sweating
- *Vascular (Extracardiac)*: thrombophlebitis
- *White Cell and Reticuloendothelial*: leukopenia, lymphadenopathy

Adverse Reactions in Pediatric Patients

Pediatric Crohn's Disease

There were some differences in the adverse reactions observed in the pediatric patients receiving infliximab compared to those observed in adults with Crohn's disease. These differences are discussed in the following paragraphs. The following adverse reactions were reported more commonly in 103 randomized pediatric Crohn's disease patients administered 5 mg/kg infliximab through 54 weeks than in 385 adult Crohn's disease patients receiving a similar treatment regimen: anemia (11%), leukopenia (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%).

Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn's and in 50% of adult patients in Study Crohn's I. In Study Peds Crohn's, infections were reported more frequently for patients who received every 8-week as opposed to every 12-week infusions (74% and 38%, respectively), while serious infections were reported for 3 patients in the every 8-week and 4 patients in the every 12-week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported for 3 patients, (2 in the every 8-week and 1 in the every 12-week maintenance treatment groups). Herpes zoster was reported for 2 patients in the every 8-week maintenance treatment group.

In Study Peds Crohn's, 18% of randomized patients experienced 1 or more infusion reactions, with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn's, there were no serious infusion reactions, and 2 patients had non-serious anaphylactoid reactions.

In Study Peds Crohn's, in which all patients received stable doses of 6-MP, AZA, or MTX, excluding inconclusive samples, 3 of 24 patients had antibodies to infliximab. Although 105 patients were tested for antibodies to infliximab, 81 patients were classified as inconclusive because they could not be ruled as negative due to assay interference by the presence of infliximab in the sample.

Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric patients in Crohn's disease clinical trials; 4% had ALT elevations $\geq 3 \times$ ULN, and 1% had elevations $\geq 5 \times$ ULN. (Median follow-up was 53 weeks).

Pediatric Ulcerative Colitis

Overall, the adverse reactions reported in the pediatric ulcerative colitis trial and adult ulcerative colitis (Study UC I and Study UC II) studies were generally consistent. In a pediatric UC trial, the most common adverse reactions were upper respiratory tract infection, pharyngitis, abdominal pain, fever, and headache.

Infections were reported in 31 (52%) of 60 treated patients in the pediatric UC trial and 22 (37%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in the pediatric UC trial was similar to that in the pediatric Crohn's disease study (Study Peds Crohn's) but higher than the proportion in the adults' ulcerative colitis studies (Study UC I and Study UC II). The overall incidence of infections in the pediatric UC trial was 13/22 (59%) in the every 8-week maintenance treatment group. Upper respiratory tract infection (7/60 [12%]) and pharyngitis (5/60 [8%]) were the most frequently reported respiratory system infections. Serious infections were reported in 12% (7/60) of all treated patients. In the pediatric UC trial, 58 patients were evaluated for antibodies to infliximab using the EIA as well as the drug-tolerant ECLIA. With the EIA, 4 of 58 (7%) patients had antibodies to infliximab. With the ECLIA, 30 of 58 (52%) patients had antibodies to infliximab *[see Adverse Reactions, Immunogenicity (6.1)]*. The higher incidence of antibodies to infliximab by the ECLIA method was due to the 60-fold higher sensitivity compared to the EIA method. While EIA-positive patients generally had undetectable trough infliximab concentrations, ECLIA-positive patients could have detectable trough concentrations of infliximab because the ECLIA assay is more sensitive and drug-tolerant.

Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 17% (10/60) of pediatric patients in the pediatric UC trial; 7% (4/60) had ALT elevations $\geq 3 \times$ ULN, and 2% (1/60) had elevations $\geq 5 \times$ ULN. (Median follow-up was 49 weeks).

Overall, 8 of 60 (13%) treated patients experienced one or more infusion reactions, including 4 of 22 (18%) patients in the every 8-week treatment maintenance group. No serious infusion reactions were reported.

In the pediatric UC trial, 45 patients were in the 12- to 17-year age group and 15 in the 6- to 11-year age group. The numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on safety events. There were higher proportions of patients with serious adverse events (40% vs. 18%) and discontinuation due to adverse events (40% vs. 16%) in the younger age group than in the older age group. While the proportion of patients with infections was also higher in the younger age group (60% vs. 49%), for serious infections, the proportions were similar in the two age groups (13% in the 6- to 11-year age group vs. 11% in the 12- to 17-year age group). Overall proportions of adverse reactions, including infusion reactions, were similar between the 6- to 11- and 12- to 17-year age groups (13%).

6.2   Postmarketing Experience

Adverse reactions have been identified during post-approval use of infliximab products in adult and pediatric patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions, some with fatal outcome, have been reported during post-approval use of infliximab products: neutropenia *[see Warnings and Precautions (5.6)]*, agranulocytosis (including infants exposed *in utero* to infliximab products), interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis and rapidly progressive disease), idiopathic thrombocytopenic purpura, thrombotic

thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), new onset and worsening psoriasis (all subtypes including pustular, primarily palmoplantar), transverse myelitis, and neuropathies (additional neurologic reactions have also been observed) *[see Warnings and Precautions (5.9)]*, acute liver failure, jaundice, hepatitis, and cholestasis *[see Warnings and Precautions (5.4)]*, serious infections *[see Warnings and Precautions (5.1)]*, malignancies, including leukemia, melanoma, Merkel cell carcinoma, and cervical cancer *[see Warnings and Precautions (5.2)]* and vaccine breakthrough infection including bovine tuberculosis (disseminated BCG infection) following vaccination in an infant exposed *in utero* to infliximab products *[see Warnings and Precautions (5.15)]*.

Infusion-related Reactions

In postmarketing experience, cases of anaphylactic reactions, including anaphylactic shock, laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with administration of infliximab products.

Cases of transient visual loss have been reported in association with infliximab products during or within 2 hours of infusion. Cerebrovascular accidents, myocardial ischemia/infarction (some fatal), and arrhythmia occurring within 24 hours of initiation of infusion have also been reported *[see Warnings and Precautions (5.8)]*.

Adverse Reactions in Pediatric Patients

The following serious adverse reactions have been reported in the postmarketing experience in children: infections (some fatal) including opportunistic infections and tuberculosis, infusion reactions, and hypersensitivity reactions.

Serious adverse reactions in the postmarketing experience with infliximab products in the pediatric population have also included malignancies, including hepatosplenic T-cell lymphomas *[see Boxed Warning and Warnings and Precautions (5.2)]*, transient hepatic enzyme abnormalities, lupus-like syndromes, and the development of autoantibodies.

7   DRUG INTERACTIONS

7.1   Use with Anakinra or Abatacept

An increased risk of serious infections was seen in clinical studies of other TNFα-blocking agents used in combination with anakinra or abatacept, with no added clinical benefit. Because of the nature of the adverse reactions seen with these combinations with TNF-blocker therapy, similar toxicities may also result from the combination of anakinra or abatacept with other TNFα-blocking agents. Therefore, the combination of AVSOLA and anakinra or abatacept is not recommended *[see Warnings and Precautions (5.10 and 5.11)]*.

7.2   Use with Tocilizumab

The use of tocilizumab in combination with biological DMARDs such as TNF antagonists, including AVSOLA, should be avoided because of the possibility of increased immunosuppression and increased risk of infection.

7.3 Use with Other Biological Therapeutics

The combination of AVSOLA with other biological therapeutics used to treat the same conditions as AVSOLA is not recommended *[see Warnings and Precautions (5.12)]*.

7.4 Methotrexate (MTX) and Other Concomitant Medications

Specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides MTX were non-steroidal anti-inflammatory agents (NSAIDs), folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications included MTX in approximately half of the patients as well as NSAIDs, folic acid and corticosteroids. Concomitant MTX use may decrease the incidence of anti-drug antibody production and increase infliximab product concentrations.

7.5 Immunosuppressants

Patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants *[see Adverse Reactions (6.1)]*. Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates.

7.6 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-1, IL-6, IL-10, IFN) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as infliximab products, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of AVSOLA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

7.7 Live Vaccines/Therapeutic Infectious Agents

It is recommended that live vaccines not be given concurrently with AVSOLA. It is also recommended that live vaccines not be given to infants after *in utero* exposure to infliximab products for at least 6 months following birth *[see Warnings and Precautions (5.15)]*.

It is recommended that therapeutic infectious agents not be given concurrently with AVSOLA *[see Warnings and Precautions (5.15)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published literature on the use of infliximab products during pregnancy have not reported a clear association with infliximab products and adverse pregnancy outcomes. Infliximab products cross the placenta and infants exposed *in utero* should not be administered live vaccines for at least 6 months

after birth (see *Clinical Considerations*). In a development study conducted in mice using an analogous antibody, no evidence of maternal toxicity, embryotoxicity or teratogenicity was observed (see *Data*).

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

Clinical Considerations
Fetal/neonatal adverse reactions
Infliximab products cross the placenta, and have been detected in the serum of infants up to 6 months following birth. Consequently, these infants may be at increased risk of infection, including disseminated infection which can become fatal. At least a six-month waiting period following birth is recommended before the administration of live vaccines (e.g. BCG vaccine or other live vaccines, such as the rotavirus vaccine) to these infants [see *Warnings and Precautions* (5.15)]. Cases of agranulocytosis in infants exposed *in utero* have also been reported [see *Adverse Reaction*s (6.2)].

Data

Animal Data
Because infliximab products do not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with infliximab products. An embryofetal development study was conducted in pregnant mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. This antibody, administered during the period of organogenesis on gestation day 6 and 12 at IV doses up to 40 mg/kg produced no evidence of maternal toxicity, embryotoxicity, or teratogenicity. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness.

8.2   Lactation

Risk Summary

Available information is insufficient to inform the amount of infliximab products present in human milk, and the effects on the breastfed infant. There are no data on the effects of infliximab products on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for an infliximab product and any potential adverse effects on the breastfed infant from infliximab products or from the underlying maternal condition.

8.4   Pediatric Use

The safety and effectiveness of infliximab products have been established in pediatric patients 6 to 17 years of age for induction and maintenance treatment of Crohn's disease or ulcerative colitis. However, infliximab products have not been studied in children with Crohn's disease or ulcerative colitis <6 years of age.

Pediatric Crohn's Disease

AVSOLA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response

to conventional therapy *[see Boxed Warning, Warnings and Precautions (5), Indications and Usage (1.2), Dosage and Administration (2.2), Clinical Studies (14.2) and Adverse Reactions (6.1)]*.

Infliximab has been studied only in combination with conventional immunosuppressive therapy in pediatric Crohn's disease. The longer term (greater than 1 year) safety and effectiveness of infliximab products in pediatric Crohn's disease patients have not been established in clinical trials.

Pediatric Ulcerative Colitis

The safety and effectiveness of infliximab products for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients aged 6 years and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy are supported by evidence from adequate and well-controlled studies of infliximab in adults. Additional safety and pharmacokinetic data were collected in 60 pediatric patients aged 6 years and older *[see Clinical Pharmacology (12.3), Dosage and Administration (2.4), Adverse Reactions (6.1), and Clinical Studies (14.4)]*. The effectiveness of infliximab in inducing and maintaining mucosal healing could not be established. Although 41 patients had a Mayo endoscopy subscore of 0 or 1 at the Week 8 endoscopy, the induction phase was open-label and lacked a control group. Only 9 patients had an optional endoscopy at Week 54.

In the pediatric UC trial, approximately half of the patients were on concomitant immunomodulators (AZA, 6-MP, MTX) at study start. Due to the risk of HSTCL, a careful risk-benefit assessment should be made when AVSOLA is used in combination with other immunosuppressants.

The longer term (greater than 1 year) safety and effectiveness of infliximab products in pediatric ulcerative colitis patients have not been established in clinical trials.

Juvenile Rheumatoid Arthritis (JRA)

The safety and efficacy of infliximab in patients with juvenile rheumatoid arthritis (JRA) were evaluated in a multicenter, randomized, placebo-controlled, double-blind study for 14 weeks, followed by a double-blind, all-active treatment extension, for a maximum of 44 weeks. Patients with active JRA between the ages of 4 and 17 years who had been treated with MTX for at least 3 months were enrolled. Concurrent use of folic acid, oral corticosteroids (≤0.2 mg/kg/day of prednisone or equivalent), NSAIDs, and/or disease-modifying antirheumatic drugs (DMARDs) was permitted.

Doses of 3 mg/kg infliximab or placebo were administered intravenously at Weeks 0, 2 and 6. Patients randomized to placebo crossed over to receive 6 mg/kg infliximab at Weeks 14, 16, and 20, and then every 8 weeks through Week 44. Patients who completed the study continued to receive open-label treatment with infliximab for up to 2 years in a companion extension study.

The study failed to establish the efficacy of infliximab in the treatment of JRA. Key observations in the study included a high placebo response rate and a higher rate of immunogenicity than what has been observed in adults. Additionally, a higher rate of clearance of infliximab was observed than had been observed in adults *[see Clinical Pharmacology (12.3)]*.

A total of 60 patients with JRA were treated with doses of 3 mg/kg and 57 patients were treated with doses of 6 mg/kg. The proportion of patients with infusion reactions who received 3 mg/kg infliximab was 35% (21/60) over 52 weeks compared with 18% (10/57) in patients who received 6 mg/kg over 38 weeks. The most common infusion reactions reported were vomiting, fever, headache, and hypotension. In the 3 mg/kg infliximab group, 4 patients had a serious infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among the serious infusion reactions). In the 6 mg/kg infliximab group, 2 patients

had a serious infusion reaction, 1 of whom had a possible anaphylactic reaction. Two of the 6 patients who experienced serious infusion reactions received infliximab by rapid infusion (duration of less than 2 hours). Antibodies to infliximab developed in 38% (20/53) of patients who received 3 mg/kg infliximab compared with 12% (6/49) of patients who received 6 mg/kg.

A total of 68% (41/60) of patients who received 3 mg/kg infliximab in combination with MTX experienced an infection over 52 weeks compared with 65% (37/57) of patients who received 6 mg/kg infliximab in combination with MTX over 38 weeks.

The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was pneumonia. Other notable infections included primary varicella infection in 1 patient and herpes zoster in 1 patient.

8.5   Geriatric Use

In rheumatoid arthritis and plaque psoriasis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque psoriasis, aged 65 or older who received infliximab, compared to younger patients-although the incidence of serious adverse reactions in patients aged 65 or older was higher in both infliximab and control groups compared to younger patients. In Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. There is a greater incidence of infections in the elderly population in general. The incidence of serious infections in infliximab-treated patients 65 years and older was greater than in those under 65 years of age; therefore caution should be used in treating the elderly *[see Adverse Reactions (6.1)]*.

10   OVERDOSAGE

Single doses up to 20 mg/kg of infliximab have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

11   DESCRIPTION

Infliximab-axxq, the active ingredient in AVSOLA, is a chimeric IgG1κ monoclonal antibody (composed of human constant and murine variable regions) specific for human tumor necrosis factor-alpha (TNFα). It has a molecular weight of approximately 149.1 kilodaltons. Infliximab-axxq is produced in a recombinant Chinese Hamster Ovary (CHO) cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

AVSOLA is supplied as a sterile, white to slightly yellow, lyophilized powder for intravenous infusion. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-dose vial contains 100 mg infliximab-axxq, dibasic sodium phosphate, anhydrous (4.9 mg), monobasic sodium phosphate, monohydrate (2.2 mg), polysorbate 80 (0.5 mg), and sucrose (500 mg).

No preservatives are present.

12   CLINICAL PHARMACOLOGY

12.1   Mechanism of Action

Infliximab products neutralize the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibit binding of TNFα with its receptors. Infliximab products do not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab products can be lysed *in vitro* or *in vivo*. Infliximab products inhibit the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T-lymphocytes and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which infliximab products exert their clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab products prevent disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allow eroded joints to heal.

12.2   Pharmacodynamics

Elevated concentrations of TNFα have been found in involved tissues and fluids of patients with rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. In rheumatoid arthritis, treatment with infliximab products reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemoattraction [IL-8 and monocyte chemotactic protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3]. In Crohn's disease, treatment with infliximab products reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon. After treatment with infliximab products, patients with rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to baseline. Peripheral blood lymphocytes from patients treated with infliximab products showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients. In psoriatic arthritis, treatment with infliximab products resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin lesions as well as a reduction of macrophages in the synovium. In plaque psoriasis, infliximab product treatment may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which infliximab products exert their clinical effects is unknown.

12.3   Pharmacokinetics

In adults, single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg of infliximab showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis, 5 mg/kg in Crohn's disease, and 3 mg/kg to 5 mg/kg in plaque psoriasis indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days.