IXIFI™
Infliximab

1. NAME OF THE MEDICINAL PRODUCT

IXIFI Powder for Concentrate for Solution for Infusion 100 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single dose vial contains 100 mg of infliximab in a 15 mL vial. After reconstitution with 10 mL of Sterile Water for Injection, each mL contains 10 mg of infliximab.

Infliximab, the active ingredient in IXIFI, is a chimeric IgG1κ monoclonal antibody (composed of human constant and murine variable regions) specific for human tumor necrosis factor-alpha (TNFα), with an identical amino acid sequence for the variable and constant regions and identical primary structure with Remicade (infliximab), the reference product. It has a molecular weight of approximately 149 kilodaltons. The manufacturing process for infliximab drug substance uses a recombinant Chinese hamster ovary (CHO) cell line that contains the DNA encoding the sequence for infliximab and is grown in suspension culture using chemically-defined (CD), animal-derived component-free (ACF) media.

3. PHARMACEUTICAL FORM

White, lyophilized powder for intravenous (IV) infusion.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Rheumatoid Arthritis (RA)

IXIFI, in combination with methotrexate (MTX), is indicated for:
The reduction of signs and symptoms as well as the improvement in physical function in

- adult patients with active disease when the response to disease-modifying drugs, including MTX, has been inadequate.
- adult patients with severe, active and progressive disease not previously treated with MTX or other disease-modifying anti-rheumatic drugs (DMARDs).

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated (see Section 5.1).

Crohn's Disease

IXIFI is indicated for:

- Treatment of moderately to severely, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
- Treatment of fistulizing Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics,

drainage and immunosuppressive therapy).

Pediatric Crohn's Disease

IXIFI is indicated for:
Treatment of severe, active Crohn's disease, in pediatric patients aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy.

Ulcerative Colitis

IXIFI is indicated for:
Treatment of moderately to severely active ulcerative colitis (UC) in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Pediatric Ulcerative Colitis

IXIFI 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 UC who have had an inadequate response to conventional therapy.

Ankylosing Spondylitis

IXIFI is indicated for:
Treatment of ankylosing spondylitis, in adult patients who have severe axial symptoms, elevated serological markers of inflammatory activity and who have responded inadequately to conventional therapy.

Psoriatic Arthritis

IXIFI, in combination with MTX, is indicated for:
Treatment of active and progressive psoriatic arthritis in adult patients who have responded inadequately to DMARDs.

Psoriasis

IXIFI is indicated for:
Treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA (see Section 5.1).

4.2. Posology and method of administration

IXIFI treatment is to be administered under the supervision and monitoring of specialized physicians experienced in the diagnosis and treatment of rheumatoid arthritis, inflammatory

bowel diseases, ankylosing spondylitis, psoriatic arthritis or psoriasis. IXIFI should be administered intravenously.

During IXIFI treatment, other concomitant therapies, e.g., corticosteroids and immunosuppressants should be optimized.

Posology

Dosage - Adults (≥ 18 years)

IXIFI is administered by intravenous infusion.

Rheumatoid Arthritis

3 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

IXIFI must be given concomitantly with MTX.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Moderately to Severely, Active Crohn's Disease

5 mg/kg given as an intravenous infusion over a 2-hour period. Available data do not support further infliximab treatment, in patients not responding within 2 weeks to the initial infusion. In responding patients, the strategy for continued treatment is:

- Maintenance: Additional infusions of 5 mg/kg at 2 and 6 weeks after the initial dose, followed by infusions every eight weeks.

Fistulizing Crohn's Disease

An initial 5 mg/kg infusion given over a 2-hour period is to be followed with additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion. If a patient does not respond after these 3 doses, no additional treatment with infliximab should be given.

In responding patients, the strategies for continued treatment are:

- Additional infusions of 5 mg/kg every 8 weeks or
- Re-administration if signs and symptoms of the disease recur followed by infusions of 5 mg/kg every 8 weeks (see *Re-administration* below and Section 4.4).

Ulcerative Colitis

5 mg/kg given as intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. three doses. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Ankylosing Spondylitis

5 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. If a patient does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be given.

Psoriatic Arthritis

5 mg/kg given as intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Efficacy and safety have been demonstrated in combination with MTX.

Psoriasis

5 mg/kg given as intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient shows no response after 14 weeks (i.e. after 4 doses), no additional treatment with infliximab should be given.

Re-administration for Crohn's Disease and Rheumatoid Arthritis

If the signs and symptoms of disease recur, IXIFI can be re-administered within 16 weeks following the last infusion. In clinical studies, delayed hypersensitivity reactions have been uncommon and have occurred after drug-free intervals of less than 1 year (see Sections 4.4 and 4.8, *Delayed Hypersensitivity*). After a drug-free interval of 16 weeks to 2 years, the risk of delayed hypersensitivity following re-administration is not known. Therefore, after a drug-free interval of 16 weeks, re-administration is not recommended.

Re-administration for Ulcerative Colitis

The safety and efficacy of re-administration, other than every 8 weeks, has not been established (see Sections 4.4 and 4.8).

Re-administration for Ankylosing Spondylitis

The safety and efficacy of re-administration, other than every 6 to 8 weeks, has not been established (see Sections 4.4 and 4.8).

Re-administration for Psoriatic Arthritis

The safety and efficacy of re-administration, other than every 8 weeks, has not been established (see Sections 4.4 and 4.8).

Re-administration for Psoriasis

Limited experience from retreatment with one single infliximab dose in psoriasis after an interval of 20 weeks suggests reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared to the initial induction regimen (see Section 5.1).

Special populations

Pediatrics (6-17 years of age)

IXIFI has not been studied in children with Crohn's disease or UC < 6 years of age. The pharmacokinetics of infliximab has been evaluated in pediatric patients with Crohn's disease and UC (see Section 5.2). The safety and effectiveness of IXIFI in pediatric patients with juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis have not been established.

Pediatric Crohn's Disease

5 mg/kg given as intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. For some patients a longer dosing interval may be sufficient. Available data do not support further infliximab treatment in pediatric patients not responding within the first 10 weeks of treatment.

Pediatric Crohn's disease patients who have had their dose adjusted to greater than 5 mg/kg every 8 weeks, may be at greater risk for adverse reactions. Continued therapy with the adjusted dose should be carefully considered in patients who show no evidence of additional therapeutic benefit after dose adjustment.

Pediatric Ulcerative Colitis

5 mg/kg given as intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Renal Impairment

IXIFI has not been studied in patients with renal impairment. No dose recommendations can be made (see Section 5.2).

Hepatic Impairment

IXIFI has not been studied in patients with hepatic impairment. No dose recommendations can be made (see Section 5.2).

Administration

IXIFI infusions should be administered by qualified healthcare professionals.

IXIFI should be administered intravenously over a 2-hour period. All patients administered IXIFI are to be observed for at least 1-2 hours post-infusion for acute infusion-related

reactions. Prior to treatment, ensure appropriate personnel and medication, such as adrenaline, antihistamines and corticosteroids, and an artificial airway must be available to treat reactions (e.g., hypersensitivity, other reactions) that occur during infusion and shortly after infusion. Patients may be pre-treated with e.g., histamine-1 receptor antagonists, histamine-2 receptor antagonists, hydrocortisone and/or paracetamol and infusion rate may be slowed in order to decrease the risk of infusion-related reactions especially if infusion-related reactions have occurred previously (see Section 4.4). Discontinue the infusion if the mild to moderate reactions reoccur.

Discontinue the infusion if severe hypersensitivity reactions occur during the infusion.

Shortened Infusion Across Adult Indications

In carefully selected adult patients who have tolerated at least 3 initial 2-hour infusions of IXIFI (induction phase) and are receiving maintenance therapy, consideration may be given to administering subsequent infusions over a period of not less than 1 hour. If an infusion reaction occurs in association with a shortened infusion, a slower infusion rate may be considered for future infusions if treatment is to be continued. Shortened infusions at doses > 6 mg/kg have not been studied.

For preparation and administration instructions, see Section 6.6.

4.3. Contraindications

IXIFI is contraindicated in patients with a previous severe hypersensitivity reaction to infliximab products or any of the inactive ingredients of IXIFI (see Section 6.1) or any murine proteins [severe hypersensitivity reactions have included anaphylaxis, hypotension, and serum sickness] (see Sections 4.4 and 4.8).

IXIFI is contraindicated in patients with moderate or severe heart failure (New York Heart Association [NYHA] Functional Class III/IV) (see Sections 4.4 and 4.8).

IXIFI is contraindicated in patients with tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections (see Section 4.4).

4.4. Special warnings and precautions for use

IXIFI is a biosimilar medicinal product. The prescribing physician should be involved in any decision regarding its interchangeability. In order to improve the traceability of biological medicinal products, the trademark and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Before starting treatment with IXIFI, patients must be evaluated for both active and inactive (‘latent’) tuberculosis (see *Infections*).

IXIFI should be used with caution in patients with mild heart failure (NYHA Class I/II) (see *Heart Failure*).

Infusion Reactions and Hypersensitivity

Infliximab has been associated with acute infusion-related reactions, including, anaphylactic shock, and delayed hypersensitivity reactions (see Section 4.8). To minimize the incidence of hypersensitivity reactions, including infusion reactions and serum sickness-like reactions, IXIFI should be administered as regular maintenance therapy after an induction regimen at weeks 0, 2 and 6 (see Section 4.2).

Acute infusion reactions including anaphylactic reactions may develop during (within seconds) or within a few hours following infusion. If acute infusion reactions occur, the infusion must be interrupted immediately. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available (see Section 4.2). Patients may be pretreated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.

Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions. A low proportion of the infusion reactions were serious allergic reactions. In Crohn's disease patients, an association between development of antibodies to infliximab and reduced duration of response has also been observed. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and a reduction in the frequency of infusion reactions. The effect of concomitant immunomodulator therapy was more profound in episodically treated patients than in patients given maintenance therapy. Patients who discontinue immunosuppressants prior to or during IXIFI treatment are at greater risk of developing these antibodies. Antibodies to infliximab cannot always be detected in serum samples. If serious reactions occur, symptomatic treatment must be given and further IXIFI infusions must not be administered (see Section 4.8, *Immunogenicity*).

In clinical trials, delayed hypersensitivity reaction has been reported. Available data suggest an increased risk for delayed hypersensitivity with increasing drug-free interval. Advise patients to seek immediate medical advice if they experience any delayed adverse event (see Section 4.8, *Delayed Hypersensitivity*). If patients are retreated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.

Infusion Reactions Following Re-administration of IXIFI

In a psoriasis clinical trial, a 3-dose re-induction of infliximab after a period of no treatment resulted in a higher incidence of serious infusion reactions during the re-induction regimen (see Section 4.8) than had been observed in rheumatoid arthritis, psoriasis, and Crohn's disease trials in which a period of no drug treatment was followed by regular maintenance therapy without re-induction.

In the case where IXIFI maintenance therapy for psoriasis is interrupted, IXIFI should be reinitiated as a single dose followed by maintenance therapy.

In general, the benefit-risk of re-administration of IXIFI after a period of no-treatment, especially as a re-induction regimen given at weeks 0, 2, and 6, should be carefully considered.

Infections

Patients must be monitored closely for infections including tuberculosis before, during and after treatment with IXIFI. Because the elimination of infliximab may take up to six months, monitoring should be continued throughout this period. Further treatment with IXIFI must not be given if a patient develops a serious infection or sepsis.

IXIFI should not be given to patients with a clinically important, active infection. Caution should be exercised when considering the use of IXIFI in patients with chronic infection or a history of recurrent infections, including use of concomitant immunosuppressive medications. Patients should be advised of and avoid exposure to potential risk factors for infection as appropriate.

Tumor necrosis factor-alpha (TNFα) mediates inflammation and modulates cellular immune responses. Experimental data show that TNFα is essential for the clearing of intracellular infections. Clinical experience shows that host defense against infection is compromised in some patients treated with infliximab.

It should be noted that suppression of TNFα may also mask symptoms of infection such as fever. Early recognition of atypical clinical presentations of serious infections is critical in order to minimize delays in diagnosis and treatment.

Patients taking TNF blockers are more susceptible to serious infections. Mycobacterial (including tuberculosis [frequently disseminated or extrapulmonary at clinical presentation]), viral infections, bacterial infections, including sepsis and pneumonia, invasive fungal infections, and other opportunistic infections have been observed in patients treated with infliximab. Some of these infections have been fatal. Opportunistic infections reported in patients on infliximab have included, but are not limited to pneumocystosis, histoplasmosis, cytomegalovirus infection, atypical mycobacterial infections, listeriosis and aspergillosis. In clinical trials, infections have been reported more frequently in pediatric patient populations than in adult populations (see Section 4.8).

Tuberculosis
Before starting treatment with IXIFI, all patients must be evaluated for both active and inactive (‘latent’) tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e. tuberculin skin test and chest X-ray, should be performed in all patients (local recommendations may apply). Prescribers are reminded of the risk of false negative tuberculin skin test results especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, IXIFI therapy must not be initiated (see Section 4.3).

If inactive (‘latent’) tuberculosis is diagnosed, prophylactic anti-tuberculosis therapy must be started before the initiation of IXIFI, and in accordance with local recommendations. In this situation, the benefit/ risk balance of IXIFI therapy should be very carefully considered.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, anti-tuberculosis therapy should be considered before the initiation of IXIFI. Use of anti-tuberculosis therapy should also be considered before the initiation of

IXIFI in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Use of anti-tuberculosis therapy should be considered before the initiation of IXIFI in patients who have several or highly significant risk factors for tuberculosis infection and have a negative test for latent tuberculosis.

The decision to initiate anti-tuberculosis therapy in these patients should only be made following consultation with a physician with expertise in the treatment of tuberculosis and taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy.

Cases of active tuberculosis have occurred in patients treated with infliximab during and after treatment for latent tuberculosis. Cases of active tuberculosis including miliary tuberculosis and tuberculosis with extrapulmonary location have been reported in patients treated with infliximab.

All patients should be informed to seek medical advice if signs / symptoms suggestive of tuberculosis (e.g., persistent cough, wasting / weight loss, low-grade fever) appear during or after IXIFI treatment.

Invasive Fungal Infections
For patients who have resided in or traveled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of IXIFI treatment should be carefully considered before initiation or continuation of IXIFI therapy.

In patients treated with IXIFI, an invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if they develop a serious systemic illness. Invasive fungal infections may present as disseminated rather than localized disease, and antigen and antibody testing may be negative in some patients with active infection. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. The decision to administer empiric antifungal therapy should be made, if feasible, 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.

Fistulizing Crohn's Disease
Patients with fistulizing Crohn's disease with acute suppurative fistulas must not initiate IXIFI therapy until a source for possible infection, specifically abscess, has been excluded (see Section 4.3).

Hepatitis B Reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF blocker including infliximab, who are chronic carriers of this virus. Some cases have had fatal outcome. Patients at risk for Hepatitis B Virus (HBV) infection should be evaluated for prior evidence of HBV infection before initiating IXIFI therapy. Carriers of HBV who require treatment with IXIFI should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data

of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, IXIFI should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated. Patients should be tested for HBV infection before initiating treatment with immunosuppressants, including IXIFI. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Hepatobiliary Events

Cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of infliximab. Isolated cases of liver failure resulting in liver transplantation or death have occurred. A causal relationship between infliximab and these events has not been established. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or alanine aminotransferase (ALT) elevations ≥ 5 times the upper limit of normal develops, IXIFI should be discontinued, and a thorough investigation of the abnormality should be undertaken.

Concurrent Administration with Other Biological Therapeutics

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNF blocker, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with concurrent use of etanercept and anakinra therapy, similar toxicities may also result from the concurrent use of anakinra and other TNF blockers. Therefore, the concurrent use of IXIFI and anakinra is not recommended.

In clinical studies, concurrent administration of TNF blockers and abatacept have been associated with an increased risk of infections including serious infections compared with TNF blockers alone, without increased clinical benefit. Because of the nature of the adverse events seen with the concurrent use of TNF blockers and abatacept therapy, the concurrent use of infliximab and abatacept is not recommended.

There is insufficient information regarding the concurrent use of infliximab products with other biological products used to treat the same conditions as IXIFI. The concurrent use of IXIFI with these biological products is not recommended because of the possibility of an increased risk of infection and other potential pharmacological interactions.

Switching Between Biological DMARDs

When switching from one biologic to another, patients should continue to be monitored, since overlapping biological activity may further increase the risk of infection.

Vaccinations

Prior to initiating IXIFI in pediatric and adult patients, update vaccinations in accordance with current vaccination guidelines.

Live Vaccines/Therapeutic Infectious Agents

In patients receiving TNF blockers, 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 IXIFI is not recommended.

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 IXIFI.

Infants Exposure *in Utero*

Fatal outcome due to disseminated Bacille Calmette-Guérin (BCG) infection has been reported in an infant who received BCG vaccine after *in utero* exposure to infliximab. A 12-month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab, unless infliximab exposure was limited to the first trimester or if infant infliximab serum levels are undetectable. Administration of a live vaccine prior to 12 months of age might be considered if the benefit of the vaccination clearly outweighs the theoretical risk of administration of live vaccines to the infants (see Section 4.6).

Infants Exposure Via Breast Milk

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see Section 4.6).

Non-live Vaccines

In a subset of patients from the ASPIRE study, a similar proportion of patients in each treatment group mounted an effective two-fold increase in titers to a polyvalent pneumococcal vaccine, indicating that infliximab did not interfere with T-cell independent humoral immune responses.

Autoimmune Processes

The relative deficiency of TNFα caused by TNF blocker therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with IXIFI and is positive for antibodies against double-stranded DNA, further treatment with IXIFI must not be given (see Section 4.8, *Antinuclear Antibodies (ANA)/Anti-double-stranded DNA (dsDNA) Antibodies*).

Neurological Events

Infliximab and other agents that inhibit TNFα have been associated with 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 (see Section 4.8).

Prescribers should exercise caution in considering the use of IXIFI in patients with these neurologic disorders and should consider discontinuation of IXIFI if these disorders develop.

Malignancies and Lymphoproliferative Disorders

In the controlled portions of clinical trials of all the TNF blockers, more cases of malignancies including lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During clinical trials of infliximab across all approved indications, the incidence of lymphoma in infliximab-treated subjects was higher than expected in the general population, but the occurrence of lymphoma was rare. Patients with Crohn's disease or rheumatoid arthritis, 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 blocker therapy.

Non-lymphoma Malignancy
In an exploratory clinical trial evaluating the use of infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Caution should be exercised in considering treatment of patients with increased risk of malignancy due to heavy smoking.

Caution should also be exercised in patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment.

Psoriasis patients should be monitored for non-melanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment.

Pediatric Malignancy
Post-marketing cases of malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) who received TNF blockers (initiation of therapy ≤ 18 years of age), including infliximab, to treat Juvenile Idiopathic Arthritis (JIA), Crohn’s disease or other conditions. Approximately half the reports were lymphomas. The other cases represented a variety of different malignancies and included malignancies that are not usually observed in children and adolescents. Most of the patients were receiving concomitant immunosuppressants, such as methotrexate, azathioprine or 6-mercaptopurine. The role of TNF blockers in the development of malignancies in children and adolescents remains unclear.

Hepatosplenic T-cell Lymphoma (HSTCL)
Post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF blockers including infliximab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with or immediately prior to a TNF blocker. The vast majority of infliximab cases have occurred in patients with Crohn’s disease or ulcerative colitis and most were reported in adolescent or young adult males. Cases of HSTCL have also occurred in Crohn's disease patients and ulcerative colitis patients receiving azathioprine or 6-mercaptopurine who were not treated with infliximab. Before initiating or continuing IXIFI therapy in a patient who is receiving an immunosuppressant such as azathioprine or 6-mercaptopurine, the need for continuing the immunosuppressant

therapy should be carefully assessed in light of the potential risks of concomitant therapy. The causal relationship of HSTCL to infliximab therapy remains unclear.

A risk for the development for HSTCL in patients treated with IXIFI cannot be excluded (see Sections 4.2 and 4.8).

All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before the therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. With current data, it is not known if infliximab treatment influences the risk for developing dysplasia or colon cancer (see Section 4.8).

Since the possibility of increased risk of cancer development in patients with newly diagnosed dysplasia treated with infliximab is not established, the risk and benefits to the individual patients must be carefully reviewed and consideration should be given to discontinuation of therapy.

Leukemia
Cases of acute and chronic leukemia have been reported with post-marketing TNF blocker use in RA and other diseases. Even in the absence of TNF blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Skin Cancers
Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including infliximab products (see Section 4.8). 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 an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age. A causal relationship between infliximab and cervical cancer cannot be excluded. Periodic screening should continue in women treated with IXIFI, including those over 60 years of age.

The potential role of TNF blocker therapy in the development of malignancies is not known. With the current knowledge, a risk for the development of lymphomas or other malignancies in patients treated with a TNF blocker cannot be excluded (see Section 4.8). Caution should be exercised when considering TNF blocker therapy for patients with history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Congestive Heart Failure

IXIFI should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and IXIFI must not be continued in patients who develop new or worsening symptoms of heart failure (see Sections 4.3 and 4.8).

Hematologic Events

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 therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with IXIFI 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 IXIFI. Discontinuation of IXIFI therapy should be considered in patients who develop significant hematologic abnormalities.

Pediatrics

IXIFI has not been studied in patients with Crohn's disease or ulcerative colitis below the age of 6 years.

Use in Elderly

The pharmacokinetics of infliximab in elderly patients has not been studied. The incidence of serious infections in infliximab-treated geriatric patients was greater than in infliximab-treated younger adult patients; therefore, close monitoring of geriatric patients for development of serious infections is recommended.

Others

Studies have not been performed in patients with liver or renal disease (see Section 5.2).

There are insufficient preclinical data to draw conclusions on the effects of infliximab on fertility and general reproductive function (see Section 5.3).

There is limited safety experience of surgical procedures in infliximab-treated patients. The long half-life of IXIFI should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on IXIFI should be closely monitored for infections, and appropriate actions should be taken.

There is limited safety experience of infliximab treatment in patients who have undergone arthroplasty.

Treatment of patients with intestinal strictures due to Crohn's disease is not recommended since the risk/benefit relationship in this patient population has not been established.

4.5. Interaction with other medicinal products and other forms of interaction

Specific drug interaction studies have not been conducted with IXIFI.

In rheumatoid arthritis and Crohn's disease patients, there are indications that concomitant use of methotrexate and other immunomodulators reduces the formation of antibodies against infliximab and increases the plasma concentrations of infliximab. However, the results are uncertain due to limitations in the methods used for serum analyses of infliximab and antibodies against infliximab.

Corticosteroids do not appear to affect the pharmacokinetics of infliximab to a clinically relevant extent.

The combination of IXIFI with other biological therapeutics used to treat the same conditions as IXIFI, including anakinra and abatacept, is not recommended (see Section 4.4).

Live Vaccines/Therapeutic Infectious Agents

It is recommended that live vaccines not be given concurrently with IXIFI. It is also recommended that live vaccines not be given to infants after *in utero* exposure to infliximab for 12 months following birth, unless infliximab exposure was limited to the first trimester or if infant infliximab serum levels are undetectable. Administration of a live vaccine prior to 12 months of age might be considered if the benefit of the vaccination clearly outweighs the theoretical risk of administration of live vaccines to the infants (see Section 4.4).

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see Sections 4.4 and 4.6).

It is recommended that therapeutic infectious agents not be given concurrently with IXIFI (see Section 4.4).

4.6. Fertility, pregnancy and lactation

Pregnancy

Infliximab products should be given to a pregnant woman only if clearly needed.

Published data suggest that there is an increased risk of adverse pregnancy outcomes in women with inflammatory bowel disease (IBD) or rheumatoid arthritis associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2.5 kg) and small for gestational age at birth.

No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Infliximab has 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.

Women of childbearing potential should use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last infliximab treatment.

Two prospective cohort studies were conducted assessing birth outcomes as well as the health status of infants up to the age of one year in women exposed to infliximab compared to non-biologic comparators including methotrexate, azathioprine, 6-mercaptopurine and systemic corticosteroids used for the treatment of similar diseases. The first study was conducted in an IBD pregnancy registry in the United States and assessed pregnancy outcomes in 294 women with inflammatory bowel disease exposed to infliximab during pregnancy compared with 515 women on a non-biologic treatment. Infliximab exposure was

not associated with increased rates of major congenital malformations, miscarriage/stillbirth, infants of low birth weight, small for gestational age, or infection in the first year of life. The second study among IBD and non-IBD patients in Sweden, Finland, and Denmark compared 97, 7, and 166 women exposed to infliximab to 2693, 2499, and 1268 women on non-biologic systemic therapy, respectively. In this study, comparing pooled data across the three countries, exposure to infliximab was not associated with increased rates of congenital anomalies or infant death. Infliximab in combination with immunosuppressants (mainly systemic corticosteroids and azathioprine) was associated with increased rates of preterm birth, small for gestational age, low birth weight, and infant hospitalization for infection compared with non-biologic systemic treatment. Although the study did not show any associations with infliximab monotherapy, the analyses could have been underpowered to detect an association.

There were additional methodological limitations with these studies that may account for the study findings in both studies: the concomitant use of other medications or treatments was not controlled and disease severity was not assessed; in the U.S. study, patient reported outcomes were collected without clinical validation. These methodological limitations hinder interpretation of the study results.

As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been detected in the serum of infants up to 12 months following birth. The clinical significance of low serum levels of infliximab on the immune status in infants is unknown. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including disseminated infection that can become fatal. At least a 12-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 Section 4.4).

Cases of agranulocytosis in infants exposed *in utero* have also been reported (see Section 4.8).

Breastfeeding

Infliximab has been detected at low levels in human milk and in infant serum via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Limited data from published literature reported that infants exposed to infliximab through breast milk had no increase in rates of infections and developed normally. The consideration of infliximab use during breastfeeding should take into account the importance of the drug to the mother and health benefits of breastfeeding for the infant.

Fertility

It is not known whether infliximab can impair fertility in humans. No impairment of fertility or reproductive performance indices were observed in male or female mice that received cV1q, an analogous mouse antibody, at intravenous doses up to 40 mg/kg given (see Section 5.3).

4.7. Effects on ability to drive and use machines

Caution should be taken when driving or using machinery following administration of IXIFI (see Section 4.8).

4.8. Undesirable effects

Adverse reactions are adverse events that were considered to be reasonably associated with the use of infliximab based on the comprehensive assessment of the available adverse event information. A causal relationship with infliximab cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials for infliximab cannot be directly compared to rates in the clinical trials of other TNF blockers and may not predict the rates observed in clinical practice.

In clinical studies with infliximab, adverse reactions were observed in approximately 60% of infliximab-treated patients and 40% of placebo-treated patients. The adverse reactions listed in Table 1 are based on experience from clinical trials. Within the organ system classes, adverse reactions are listed under the headings of frequency using the following categories: common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1000). Infusion-related reactions were the most common adverse reactions reported. Infusion-related reactions (dyspnea, urticaria and headache) were the most common cause for discontinuation.

Table 1: Adverse Reactions in Clinical Studies

Infections and infestations		
	Common:	Viral infection (e.g., influenza, herpes infections)
	Uncommon:	Abscess, cellulitis, moniliasis, sepsis, bacterial infection, tuberculosis, fungal infection, hordeolum
Neoplasms benign, malignant and unspecified		
	Uncommon:	Basal cell carcinoma, squamous cell carcinoma
	Rare:	Lymphoma
Immune system disorders		
	Common:	Serum sickness-like reactions
	Uncommon:	Lupus-like syndrome, respiratory tract allergic reactions, anaphylactic reactions
	Rare:	Sarcoid-like reaction
Blood and lymphatic disorders		
	Uncommon:	Anemia, leukopenia, lymphadenopathy, lymphocytosis, lymphopenia, neutropenia, thrombocytopenia
Psychiatric disorders		
	Uncommon:	Depression, confusion, agitation, amnesia, apathy, nervousness, somnolence, insomnia
Nervous system disorders		
	Common:	Headache, vertigo/dizziness
	Uncommon:	Exacerbation of demyelinating disease suggestive of multiple sclerosis
	Rare:	Meningitis
Eye disorders		
	Uncommon:	Conjunctivitis, endophthalmitis, keratoconjunctivitis, periorbital edema
Cardiac disorders		
	Uncommon:	Syncope, bradycardia, palpitation, cyanosis, arrhythmia, worsening heart failure
	Rare:	Tachycardia

Vascular disorders		
	Common:	Flushing
	Uncommon:	Ecchymosis/hematoma, hot flushes, hypertension, hypotension, petechia, thrombophlebitis, vasospasm, peripheral ischemia
	Rare:	Circulatory failure
Respiratory, thoracic and mediastinal disorders		
	Common:	Upper respiratory tract infection, lower respiratory tract infection (e.g., bronchitis, pneumonia), dyspnea, sinusitis
	Uncommon:	Epistaxis, bronchospasm, pleurisy, pulmonary edema
	Rare:	Pleural effusion
Gastro-intestinal system		
	Common:	Nausea, diarrhea, abdominal pain, dyspepsia, vomiting
	Uncommon:	Constipation, gastroesophageal reflux, cheilitis, diverticulitis
	Rare:	Intestinal perforation, intestinal stenosis, gastrointestinal hemorrhage
Hepatobiliary disorders		
	Common:	Abnormal hepatic function, cholecystitis
	Rare:	Hepatitis
Skin and subcutaneous tissue disorders		
	Common:	Rash, pruritus, urticaria, increased sweating, dry skin
	Uncommon:	Fungal dermatitis/onychomycosis, eczema/ seborrhea, bullous eruption, furunculosis, hyperkeratosis, rosacea, verruca, abnormal skin pigmentation/coloration, alopecia
Musculoskeletal and connective tissue disorders		
	Uncommon:	Myalgia, arthralgia, back pain
Renal and urinary disorders		
	Uncommon:	Urinary tract infection, pyelonephritis
Reproductive system and breast disorders		
	Uncommon:	Vaginitis
General disorders and administration site conditions		
	Common:	Fatigue, chest pain, infusion-related reactions, fever
	Uncommon:	Injection site reactions, edema, pain, chills/rigors, impaired healing
	Rare:	Granulomatous lesion
Investigations		
	Common:	
	Uncommon:	Elevated hepatic transaminases Autoantibodies, complement factor abnormality

Table 2: Adverse Reactions in Post-marketing Reports

(common ≥ 1/100, < 1/10; uncommon ≥ 1/1000, < 1/100; rare ≥ 1/10,000, < 1/1000; very rare < 1/10,000, including isolated reports)

Nervous system disorders		
	Rare:	Central nervous system demyelinating disorders (such as multiple sclerosis and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), neuropathies, numbness, tingling, seizure, cerebrovascular accidents occurring within approximately 24 hours of initiation of infusion
	Very rare:	Transverse myelitis
Blood and lymphatic system disorders		
	Rare:	Pancytopenia
	Very rare:	Hemolytic anemia, idiopathic thrombocytopenia purpura, thrombotic thrombocytopenic purpura, agranulocytosis (including infants exposed *in utero* to infliximab)

Neoplasms benign, malignant and unspecified (including cysts and polyps)		
	Rare:	Hepatosplenic T-cell lymphoma (the vast majority in Crohn's Disease and ulcerative colitis: primarily adolescents and young adults), lymphoma (including non-Hodgkin's lymphoma and Hodgkin's Disease), leukemia, melanoma, cervical cancer
	Very Rare:	Pediatric malignancy, Merkel cell carcinoma
Immune system disorders		
	Uncommon:	Anaphylactic reactions
	Rare:	Anaphylactic shock, serum sickness, vasculitis
Cardiac disorders		
	Rare:	Worsening heart failure, new onset heart failure
	Very rare:	Pericardial effusion
Infections and infestations		
	Uncommon:	Sepsis
	Rare:	Opportunistic infections (such as tuberculosis, atypical mycobacteria, pneumocystis carinii pneumonia (PCP), pneumocystosis, histoplasmosis, coccidioidomycosis, aspergillosis, listeriosis and candidiasis, cryptococcosis)
	Very rare:	Salmonellosis, hepatitis B reactivation, protozoal infection, and vaccine breakthrough infection (after *in utero* exposure to infliximab)*
Respiratory, thoracic and mediastinal disorders		
	Rare:	Interstitial lung disease, including pulmonary fibrosis/interstitial pneumonitis
	Very rare:	Rapidly progressive interstitial lung disease
Gastrointestinal disorders		
	Rare:	Pancreatitis
Hepatobiliary disorders		
	Rare:	Hepatitis
	Very rare:	Hepatocellular damage, jaundice, autoimmune hepatitis, liver failure
Skin and subcutaneous tissue disorders		
	Rare:	Vasculitis (primarily cutaneous), acute generalized exanthematous pustulosis (AGEP), lichenoid reactions
	Very rare:	Toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, psoriasis including new onset and pustular (primarily palmar/plantar), linear IgA bullous dermatosis (LABD)
General disorders and administration site conditions		
	Common:	Infusion-related reactions

* including bovine tuberculosis (disseminated BCG infection), see Section 4.4.

Transient visual loss occurring during or within 2 hours of infliximab infusion have also been reported.

Myocardial ischemia/myocardial infarction and arrhythmia within 24 hours of initiation of infusion have also been reported.

Hemophagocytic lymphohistiocytosis (HLH) has been very rarely reported in patients treated with infliximab.

Infusion-related Reactions

An infusion-related reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion.

In all the clinical studies, approximate 20% of infliximab-treated patients compared with 10% of placebo-treated patients experienced an infusion-related reaction. Of infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period, Week 7 through Week 54. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period.

Approximately 3% of patients discontinued treatment due to infusion-related reactions, and all patients recovered with or without medical therapy.

In a clinical study of patients with rheumatoid arthritis (ASPIRE), study medication was administered to each patient by infusion over 2 hours for the first 3 study infusions. For patients who did not experience a serious infusion reaction with the first 3 study infusions, subsequent infusions could be shortened to not less than 40 minutes. 66% of the patients (686 out of 1040) received at least one shortened infusion of 90 minutes or less and 44% of the patients (454 out of 1040) received at least one shortened infusion of 60 minutes or less. Of the infliximab-treated patients who received at least one shortened infusion, infusion-related reactions occurred in 15% (74/494) of patients and serious infusion reactions occurred in 0.4% (2/494) of patients. Shortened infusions at doses > 6 mg/kg have not been studied.

In Phase 3 clinical studies, in patients receiving infliximab with or without concomitant immunomodulator therapy, 13-19% of patients receiving infliximab at a low infusion rate (≤ 6 mg/kg/2-hr) experienced an infusion-related reaction, compared to 15-16% of patients receiving infliximab at a high infusion rate (> 6 mg/kg/2-hr or equivalent to > 3 mg/kg/1-hr). Of patients receiving infliximab at a low infusion rate, 0.4%-0.7% experienced a serious infusion-related reaction, compared to 0.4%-0.5% of patients receiving infliximab at a high infusion rate.

In a clinical study of patients with Crohn’s disease (SONIC), infusion-related reactions occurred in 16.6% (27/163) of patients receiving infliximab monotherapy, 5.0% (9/179) of patients receiving infliximab in combination with azathioprine, and 5.6% (9/161) of patients receiving azathioprine monotherapy. One patient experienced a serious infusion reaction with infliximab monotherapy.

In post-marketing surveillance, anaphylactic-like reactions, including laryngeal/pharyngeal edema, severe bronchospasm, and seizure have been associated with infliximab administration. Transient visual loss occurring during or within 2 hours of infliximab infusion have been reported. Cerebrovascular accidents, myocardial ischemia/myocardial infarction (some fatal), and arrhythmia occurring within 24 hours of initiation of infusion have also been reported.

Infusion Reactions Following Re-administration of Infliximab

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.

A clinical study in patients with moderate to severe psoriasis was designed to assess the efficacy and safety of long-term maintenance therapy versus re-treatment with an induction regimen of infliximab (maximum of four infusions at 0, 2, 6 and 14 weeks) following disease flare. Patients did not receive any concomitant immunosuppressant therapy. In the re-treatment arm, 4% (8/219) of patients experienced a serious infusion reaction versus < 1% (1/222) on maintenance therapy. The majority of serious infusion reactions occurred during the second infusion at Week 2. The interval between the last maintenance dose and the first re-induction dose ranged from 35-231 days. Symptoms included, but were not limited to, dyspnea, urticaria, facial edema, and hypotension. In all cases, infliximab treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed Hypersensitivity

In a study where 37 of 41 patients with Crohn's disease were retreated with infliximab following a 2- to 4-year period without infliximab treatment, 10 patients experienced adverse events manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache. Patients experiencing these adverse events had not experienced infusion-related adverse events associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients who received lyophilized formulation. The clinical data are not adequate to determine if occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms improved substantially or resolved with treatment in all cases. There are insufficient data on the incidence of these events after drug-free intervals of 1 to 2 years. These events have been observed only infrequently in clinical studies and post-marketing surveillance with re-treatment intervals up to 1 year. In the 3 psoriasis studies, 1% (15/1373) of patients experienced symptoms of arthralgia, serum sickness, myalgia, fever and rash. When these occurred, they were often early in the treatment course following infliximab infusions. Infliximab treatment was discontinued and/or other treatment instituted in most cases with improvement or resolution of signs and symptoms.

In a 1-year trial with repeated infusions in patients with Crohn's disease (ACCENT I study), the incidence of serum sickness-like reactions was 2.4%.

Immunogenicity

Patients who developed antibodies to infliximab were more likely (approximately 2-3 fold) to develop infusion-related reactions. Antibodies to infliximab occurred in approximately 10% of patients given a 3-dose induction regimen followed by maintenance dosing. Use of concomitant immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and infusion-related reactions.

In clinical studies using single and multiple infliximab doses ranging from 1 to 20 mg/kg, antibodies to infliximab were detected in 140 of 980 (14%) patients with any immunosuppressant therapy, and in 92 of 383 (24%) patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, 6 of 77 (8%) patients developed antibodies to infliximab. In Crohn's disease patients who received maintenance treatment, antibodies to infliximab occurred overall in 3.3% of patients receiving immunosuppressants and in 13.3% of patients not receiving immunosuppressants. The antibody incidence was 2-3 folds higher for patients treated episodically. Due to methodological limitations, a negative assay did not exclude the presence of antibodies to infliximab. Some patients who developed high titres of antibodies to infliximab had evidence of reduced efficacy (see Section 4.4, *Infusion Reactions and Hypersensitivity*). In psoriasis patients treated with infliximab as a maintenance regimen in the absence of concomitant immunomodulators, approximately 28% developed antibodies to infliximab.

Infections

Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal infections, and other opportunistic infections have been observed in patients receiving infliximab. Some of these infections have been fatal. Opportunistic infections reported in patients on infliximab have included, but are not limited to pneumocystosis, histoplasmosis, cytomegalovirus infection, atypical mycobacterial infections, listeriosis and aspergillosis (see Section 4.4).

In clinical studies 36% of infliximab-treated patients experienced infections compared with 25% of placebo-treated patients. No increased risk of serious infections was observed with infliximab compared with placebo in Crohn's disease studies and the Phase 3 study of psoriatic arthritis. In RA trials, the incidence of serious infections including pneumonia was higher in infliximab plus methotrexate treated patients compared with methotrexate alone especially at doses of 6 mg/kg or greater (see Section 4.4). In the psoriasis studies, 1.5% of patients (average of 41.9 weeks of follow-up) receiving infliximab and 0.6% of patients (average of 18.1 weeks of follow-up) receiving placebo developed serious infections.

In post-marketing spontaneous reporting, infections are the most common serious adverse event. Some of the cases have resulted in fatal outcome. Nearly 50% of reported deaths have been associated with infection. Cases of tuberculosis, sometimes fatal, including miliary tuberculosis and tuberculosis with extrapulmonary location have been reported (see Section 4.4). In post-marketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving infliximab alone or in combination with immunosuppressive agents.

Malignancies and Lymphoproliferative Disorders

In clinical studies with infliximab in which 5706 patients were treated, representing 4990 patient-years, 5 cases of lymphomas and 24 non-lymphoma malignancies were detected as compared with no lymphomas and 1 non-lymphoma malignancy in 1600 placebo-treated patients representing 892 patient-years.

In long-term safety follow-up of clinical studies with infliximab of up to 5 years, representing 6234 patient-years (3210 patients), 5 cases of lymphoma and 38 cases of non-lymphoma malignancies were reported.

From August 1998 to August 2005, 1909 cases of suspected malignancies have been reported from post-marketing, clinical trials and registries (321 in Crohn's disease patients, 1302 in rheumatoid arthritis patients and 286 in patients with other or unknown indications). Among those there were 347 lymphoma cases. During this period, the estimated exposure is 1,909, 941 patient-years since first exposure (see Section 4.4, *Malignancies and Lymphoproliferative Disorders*).

In an explanatory clinical trial involving patients with moderate to severe COPD who were either current smoker or ex-smokers, 157 patients were treated with infliximab at doses similar to those used in RA and Crohn's disease. Nine of these patients developed malignancies, including 1 lymphoma. The median duration of follow-up was 0.8 years (incidence 5.7% [95% CI 2.65%-10.6%]). There was one reported malignancy amongst 77 control patients (median duration of follow-up 0.8 years; incidence 1.3% [95% CI 0.03%-7.0%]). The majority of the malignancies developed in the lung or head and neck.

Post-marketing cases of HSTCL have been reported in patients treated with infliximab with the vast majority of cases occurring in Crohn's disease and ulcerative colitis treated with infliximab, the majority and most of whom were adolescent or young adult males (see Section 4.4, *Malignancies and Lymphoproliferative Disorders*).

Heart Failure

In a phase 2 study aimed at evaluating infliximab in congestive heart failure (CHF), higher incidence of mortality due to worsening of heart failure were seen in patients treated with infliximab, especially those treated with the higher dose of 10 mg/kg (i.e. twice the maximum approved dose). In this trial 150 patients with NYHA Class III-IV CHF (left ventricular ejection fraction $\leq$ 35%) were treated with 3 infusions of infliximab 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 38 weeks, 9 of 101 patients treated with infliximab (2 at 5 mg/kg and 7 at 10 mg/kg) died compared to one death among the 49 patients on placebo.

There have been post-marketing reports of new onset and worsening heart failure, with and without identifiable precipitating factors (e.g., pre-existing cardiovascular disease), in infliximab-treated patients. Some of these patients have been under 50 years of age.

Antinuclear Antibodies (ANA)/Anti-double-stranded DNA (dsDNA) Antibodies

In clinical studies, approximately half of infliximab-treated patients who were ANA negative at baseline developed a positive ANA during the trial (compared with approximately one-fifth placebo-treated patients). Anti-dsDNA antibodies developed in approximately 17% of patients treated with infliximab (compared with 0% of placebo-treated patients). At the last evaluation, 57% infliximab-treated patients remained anti-dsDNA positive. Clinical signs consistent with a lupus-like syndrome remained uncommon.

Hepatobiliary Events

In clinical trials, mild or moderate elevations of ALT and aspartate aminotransferase (AST) have been observed in patients receiving infliximab without progression to severe hepatic injury. Elevations of ALT 5 x Upper Limit of Normal (ULN) have been observed (see Table 3). Elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving infliximab than in controls, both when infliximab was given as monotherapy and when it was used in combination with other immunosuppressive agents. Most aminotransferase abnormalities were transient; however, a small number of patients experienced more prolonged elevations. 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.

In post-marketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving infliximab (see Section 4.4).

Table 3: Proportion of Patients with Increased ALT Activity in Clinical Trials

Indication	Number of patients[3]		Median follow-up (weeks)[4]		Proportion of patients with increased ALT			
					≥ 3 x ULN		≥ 5 x ULN	
	placebo	infliximab	placebo	infliximab	placebo	infliximab	placebo	infliximab
Rheumatoid arthritis[1]	375	1087	58.1	58.3	3.2%	3.9%	0.8%	0.9%
Crohn's disease[2]	324	1034	53.7	54.0	2.2%	4.9%	0.0%	1.5%
Pediatric Crohn's disease	N/A	139	N/A	53.0	N/A	4.4%	N/A	1.5%
Ulcerative colitis	242	482	30.1	30.8	1.2%	2.5%	0.4%	0.6%
Pediatric Ulcerative colitis	N/A	60	N/A	49.4	N/A	6.7%	N/A	1.7%
Ankylosing spondylitis	76	275	24.1	101.9	0.0%	9.5%	0.0%	3.6%
Psoriatic arthritis	98	191	18.1	39.1	0.0%	6.8%	0.0%	2.1%
Plaque psoriasis	281	1175	16.1	50.1	0.4%	7.7%	0.0%	3.4%

[1] Placebo patients received methotrexate while infliximab patients received both infliximab and methotrexate.
[2] Placebo patients in the 2 of the 3 Phase 3 trials in Crohn's disease, ACCENT I and ACCENT II, 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 the ALT analysis. In the Phase 3b trial in Crohn's disease, SONIC, placebo patients received AZA 2.5 mg/kg/day in addition to placebo infusions.
[3] Number of patients evaluated for ALT.
[4] Median follow-up is based on patients treated.

Special Populations – Pediatrics

Pediatric Crohn's Disease Patients

The following adverse events were reported more commonly in pediatric Crohn's disease patients in the REACH trial (see Section 5.1) than in adult Crohn's disease patients; anemia (10.7%), blood in stool (9.7%), leukopenia (8.7%), flushing (8.7%), viral infection (7.8%),

neutropenia (6.8%), bone fracture (6.8%), bacterial infection (5.8%), and respiratory tract allergic reaction (5.8%). Other special considerations are discussed below.

Infusion-related Reactions

Overall, in REACH, 17.5% of randomized patients experienced 1 or more infusion reactions. There were no serious infusion reactions, and 2 subjects in REACH had non-serious anaphylactic reactions.

Immunogenicity

Antibodies to infliximab were detected in 3 (2.9%) pediatric patients.

Infections

In the REACH trial, infections were reported in 56.3% of randomized subjects treated with infliximab. Infections were reported more frequently for subjects who received every 8-week as opposed to every 12-week infusions (73.6% and 38.0% respectively), while serious infections were reported for 3 subjects in the every 8-week and 4 subjects in 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. Three cases of pneumonia (1 serious) and 2 cases of herpes zoster (both non-serious) were reported.

Pediatric Ulcerative Colitis Patients

Overall proportions of patients with adverse events and serious adverse events were generally consistent in the pediatric ulcerative colitis and adult ulcerative colitis (ACT 1 and ACT 2) studies. In the pediatric ulcerative colitis study (Study Peds UC), the most common adverse event was worsening of ulcerative colitis which was greater in patients on the every 12-week vs. the every 8-week dosing regimen. In the ACT 1 and ACT 2 studies, the most common adverse event was headache. The most common serious adverse event across these three studies was worsening of the disease under study.

Infections were reported in 31 (51.7%) of 60 treated patients in Study Peds UC and 22 (36.7%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in Study Peds UC was similar to that in the pediatric Crohn’s disease study (REACH) but higher than the proportion in the adults ulcerative colitis studies (ACT 1 and ACT 2). Unlike REACH, in which infections were reported more frequently for patients who received every 8-week as opposed to every 12-week infusions; in Study Peds UC, the overall incidence of infections was similar in the every 8-week (13/22 [59.1%]) and every 12-week (14/23 [60.9%]) maintenance treatment groups. In Study Peds UC, serious infections were reported for 3 of 22 (13.6%) patients in the every 8-week and 3 of 23 (13.0%) patients in the every 12-week maintenance treatment group. Upper respiratory tract infection (7/60 [11.7%]) and pharyngitis (5/60 [8.3%]) were the most frequently reported respiratory system infections among all treated patients. The infections occurring in more than one patient in a treatment group that required antimicrobial treatment were pharyngitis (4/60 [6.7%]), urinary tract infection (4/60 [6.7%]), and bronchitis (2/60 [3.3%]).

Overall, 8 (13.3%) of 60 treated patients experienced one or more infusion reactions, with 4 of 22 (18.2%) in the every 8-week and 3 of 23 (13.0%) in the every 12-week treatment maintenance group. No serious infusion reactions were reported. All infusion reactions were mild or moderate in intensity.

Antibodies to infliximab were detected in 4 (7.7%) patients through Week 54.

In Study Peds UC, there were more patients in the 12 to 17 year age group than in the 6 to 11 year age group (45/60 [75.0%] vs. 15/60 [25.0%]). While 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 and discontinuation due to adverse events 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, for serious infections, the proportions were similar in the two age groups. Overall proportions of adverse events and infusion reactions were similar between the 6 to 11 and 12 to 17 year age groups.

Post-marketing Experience

Post-marketing spontaneous serious adverse events with infliximab in the pediatric population have included malignancies including hepatosplenic T-cell lymphomas, transient hepatic enzyme abnormalities, lupus-like syndrome, and positive autoantibodies (see Sections 4.4 and 4.8, *Malignancies and Lymphoproliferative Disorders*).

Biosimilarity

The biosimilar development program established that IXIFI is biosimilar to Remicade. The clinical program included a single-dose three-arm comparative pharmacokinetic (PK) trial in healthy volunteers and a randomized, double-blind, active-controlled, multi-national efficacy and safety comparative trial in an indication for which Remicade is licensed. The safety results for both studies did not reveal any clinical meaningful differences between IXIFI and Remicade. The safety after transition from Remicade to IXIFI was similar to that with continuous treatment with either IXIFI or Remicade.

4.9. Overdose

Single doses up to 20 mg/kg 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Tumor Necrosis Factor-Alpha (TNF-α) Inhibitors
ATC code: L04AB02

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 inhibits binding of TNFα with its receptors. Infliximab does 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 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 its 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 prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.

Pharmacodynamics

Elevated concentrations of TNFα have been found in involved tissues and fluids of patients with RA, Crohn's disease, UC, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. In RA, 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, patients with RA or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to baseline. Peripheral blood lymphocytes from infliximab product-treated patients 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 products 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.

Biosimilarity

In Study B5371002, serum hs-CRP was assessed as the PD biomarker and a component of the American College of Rheumatology (ACR) and disease activity score (DAS) assessments. Consistent with previous findings for TNFα inhibitors, mean serum hs-CRP concentrations decreased acutely in response to IXIFI and Remicade-EU treatments, and

remained suppressed through Week 30. In the ITT population, mean changes from baseline (standard deviation) in hs-CRP were -12.2 (25.7) and -12.4 (30.0) mg/L at Week 30 for the IXIFI and Remicade-EU treatments, respectively, and were similar between the treatment arms over time.

CLINICAL STUDIES

Rheumatoid Arthritis

The efficacy of infliximab in adult patients with RA was assessed in two multicenter, randomized, double-blind, pivotal trials: ATTRACT and ASPIRE. In both studies concurrent use of stable doses of folic acid, oral corticosteroids (≤ 10 mg/day) and/or non-steroidal anti-inflammatory drugs were permitted.

The primary endpoints were the reduction of signs and symptoms as assessed by the American College of Rheumatology criteria (ACR20 for ATTRACT, landmark ACR-N for ASPIRE), the prevention of structural joint damage, and the improvement in physical function. A reduction in signs and symptoms was defined to be at least a 20% improvement (ACR20) in both tender and swollen joint counts, and in 3 of the following 5 criteria: (1) evaluator's global assessment, (2) patient's global assessment, (3) functional/disability measure, (4) visual analog pain scale and (5) erythrocyte sedimentation rate or C-reactive protein. ACR-N uses the same criteria as the ACR20, calculated by taking the lowest percent improvement in swollen joint count, tender joint count, and the median of the remaining 5 components of the ACR response. Structural joint damage (erosions and joint space narrowing) in both hands and feet was measured by the change from baseline in the total van der Heijde-modified Sharp score (0-440). The Health Assessment Questionnaire (HAQ; scale 0-3) was used to measure patients' average change from baseline scores over time, in physical function.

The ATTRACT trial evaluated responses at 30, 54 and 102 weeks in a placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with methotrexate. Approximately 50% of patients were in functional Class III. Patients received placebo, 3 mg/kg or 10 mg/kg infliximab at weeks 0, 2 and 6, and then every 4 or 8 weeks thereafter. All patients were on stable methotrexate doses (median 15 mg/week) for 6 months prior to enrolment and were to remain on stable doses throughout the study.

Results from Week 54 (ACR20, HAQ and total van der Heijde-modified Sharp score) are shown in Table 4. Higher degrees of clinical response (ACR50 and ACR70) were observed in all infliximab groups at 30 and 54 weeks compared with methotrexate alone.

A reduction in the rate of the progression of structural joint damage (erosions and joint space narrowing) was observed in all infliximab groups at 54 weeks (Table 4).

The effects observed at 54 weeks were maintained through 102 weeks. Due to a number of treatment withdrawals, the magnitude of the effect difference between infliximab and the methotrexate alone group cannot be defined.

Table 4: Effects on ACR20, Structural Joint Damage and Physical Function at Week 54

		Infliximab[b]				
	Control[a]	**3 mg/kg every 8 weeks**	**3 mg/kg every 4 weeks**	**10 mg/kg every 8 weeks**	**10 mg/kg every 4 weeks**	**All infliximab[b]**
Patients with ACR20 response/ patients evaluated (%)[c]	15/88 (17%)	36/86 (42%)	41/86 (48%)	51/87 (59%)	48/81 (59%)	176/340 (52%)
Total score[d] (van der Heijde-modified Sharp score)						
Change from baseline (Mean ± SD[c])	7.0 ± 10.3	1.3 ± 6.0	1.6 ± 8.5	0.2 ± 3.6	-0.7 ± 3.8	0.6 ± 5.9
Median[c] (Interquartile range)	4.0 (0.5, 9.7)	0.5 (-1.5, 3.0)	0.1 (-2.5, 3.0)	0.5 (-1.5, 2.0)	-0.5 (-3.0, 1.5)	0.0 (-1.8, 2.0)
Patients with no deterioration/patients evaluated (%)[c]	13/64 (20%)	34/71 (48%)	35/71 (49%)	37/77 (48%)	44/66 (67%)	150/285 (53%)
HAQ change from baseline over time[e] (patients evaluated)	87	86	85	87	81	339
Mean ± SD[c]	0.2 ± 0.3	0.4 ± 0.3	0.5 ± 0.4	0.5 ± 0.5	0.4 ± 0.4	0.4 ± 0.4

[a]: control = All patients had active RA despite treatment with stable methotrexate doses for 6 months prior to enrolment and were to remain on stable doses throughout the study. Concurrent use of stable doses of oral corticosteroids (≤ 10 mg/day) and/or non-steroidal anti-inflammatory drugs was permitted, and folate supplementation was given.
[b]: all infliximab doses given in combination with methotrexate and folate with some on corticosteroids and/or non-steroidal anti-inflammatory drugs.
[c]: $p < 0.001$, for each infliximab treatment group vs. control.
[d]: greater values indicate more joint damage.
[e]: HAQ = Health Assessment Questionnaire; greater values indicate less disability.

The ASPIRE trial evaluated responses at 54 weeks in 1004 methotrexate naïve patients with early (≤ 3 years disease duration, median 0.6 years) active rheumatoid arthritis (median swollen and tender joint count of 19 and 31, respectively). All patients received methotrexate (optimized to 20 mg/week by Week 8) and either placebo, 3 mg/kg or 6 mg/kg infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter. Results from Week 54 are shown in Table 5.

After 54 weeks of treatment, both doses of infliximab and methotrexate resulted in statistically significantly greater improvement in signs and symptoms compared to methotrexate alone as measured by the proportion of patients achieving ACR20, 50 and 70 responses.

In ASPIRE, more than 90% of patients had at least two evaluable X-rays. Reduction in the rate of progression of structure damage was observed at weeks 30 and 54 in the infliximab and methotrexate groups compared to methotrexate alone.

Table 5: Effects on ACRn, Structural Joint Damage and Physical Function at Week 54, ASPIRE

	Infliximab + MTX			
	Placebo + MTX	**3 mg/kg**	**6 mg/kg**	**Combined**
Subjects randomized	282	359	363	722
Percentage ACR improvement				
Mean ± SD[a]	24.8 ± 59.7	37.3 ± 52.8	42.0 ± 47.3	39.6 ± 50.1

Change from baseline in total van der Heijde modified Sharp score[b]				
Mean ± SD[a]	3.70 ± 9.61	0.42 ± 5.82	0.51 ± 5.55	0.46 ± 5.68
Median	0.43	0.00	0.00	0.00
Improvement from baseline in HAQ averaged over time from Week 30 to Week 54[c]				
Mean ± SD[d]	0.68 ± 0.63	0.80 ± 0.65	0.88 ± 0.65	0.84 ± 0.65

[a]: $p < 0.001$, for each infliximab treatment group vs. control.
[b]: greater values indicate more joint damage.
[c]: HAQ = Health Assessment Questionnaire; greater values indicate less disability.
[d]: $p = 0.030$ and < 0.001 for the 3 mg/kg and 6 mg/kg treatment groups respectively vs. placebo + MTX.

Adult Crohn's Disease

Induction Treatment in Moderately to Severely Active Crohn's Disease
The efficacy of a single dose treatment with infliximab was assessed in 108 adult patients with active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 ≤ 400) in a randomized, double-blinded, placebo-controlled, dose-response study. Of these 108 adult patients, 27 were treated with the recommended dosage of infliximab 5 mg/kg. All patients had experienced an inadequate response to prior conventional therapies. Concurrent use of stable doses of conventional therapies was permitted, and 92% of patients continued to receive these medications.

The primary endpoint was the proportion of patients who experienced a clinical response, defined as a decrease in CDAI by ≥ 70 points from baseline at the 4-week evaluation and without an increase in Crohn's disease medications or surgery for Crohn's disease. Patients who responded at Week 4 were followed to Week 12. Secondary endpoints included the proportion of patients in clinical remission at Week 4 (CDAI < 150) and clinical response over time.

At Week 4, following a single dose of study medication, 22/27 (81%) of infliximab-treated patients receiving a 5 mg/kg dose achieved a clinical response vs. 4/25 (16%) of the placebo-treated patients ($p < 0.001$). Also at Week 4, 13/27 (48%) of infliximab-treated patients achieved a clinical remission (CDAI < 150) vs. 1/25 (4%) of placebo-treated patients. A response was observed within 2 weeks, with a maximum response at 4 weeks. At the last observation at 12 weeks, 13/27 (48%) of infliximab-treated patients were still responding.

Maintenance Treatment in Moderately to Severely Active Crohn's Disease
The efficacy of repeated infusions with infliximab was studied in a 1-year clinical study. A total of 573 patients with active Crohn's disease (CDAI ≥ 220 ≤ 400) received a single infusion of 5 mg/kg at Week 0. Sixty-eight of these patients (12%) belonged to the population defined in the indication (see Section 4.1). 335 patients (58%) responding to the 5 mg/kg infusion at Week 2 were randomized to one of three treatment groups; a placebo maintenance group, 5 mg/kg maintenance group and 10 mg/kg maintenance group, receiving repeated infusions at Week 2, 6 and every eight weeks.

At Week 30, a significantly greater proportion of patients in the combined infliximab maintenance treatment group (42%) achieved clinical remission, compared with patients in the placebo maintenance group (21%). Median time to loss of response was 46 weeks in the combined infliximab maintenance treatment group vs. 19 weeks in the placebo maintenance

group ($p < 0.001$). Similar results were obtained in the subgroup analyses of the population defined in the indication (see Section 4.1).

Improvements in quality of life measures were seen for both the IBDQ and SF-36 scores in the infliximab maintenance groups compared with the placebo maintenance group at Week 30 ($p < 0.001$).

Infliximab with or without AZA was assessed in a randomized, double-blind, active comparator study (SONIC) of 508 adult patients with moderate to severe Crohn's disease (CDAI $\geq 220 \leq 450$) who were naïve to biologics and immunosuppressants and had a median disease duration of 2.3 years. At baseline 27.4% of patients were receiving systemic corticosteroids, 14.2% of patients were receiving budesonide, and 54.3% of patients were receiving 5-ASA compounds. Patients were randomized to receive AZA monotherapy, infliximab monotherapy, or infliximab plus AZA combination therapy. Infliximab was administered at a dose of 5 mg/kg at weeks 0, 2, 6, and then every 8 weeks. AZA was given at a dose of 2.5 mg/kg daily.

The primary endpoint of the study was corticosteroid-free clinical remission at Week 26, defined as patients in clinical remission (CDAI of < 150) who, for at least 3 weeks, had not taken oral systemic corticosteroids (prednisone or equivalent) or budesonide at a dose > 6 mg/day. For results, see Table 6. The proportions of patients with mucosal healing at Week 26 were significantly greater in the infliximab plus AZA combination (43.9%, $p < 0.001$) and infliximab monotherapy groups (30.1%, $p = 0.023$) compared to the AZA monotherapy group (16.5%).

Table 6: Percent of Patients Achieving Corticosteroid-free Clinical Remission at Week 26, SONIC

	AZA Monotherapy	**Infliximab Monotherapy**	**Infliximab + AZA Combination Therapy**
Week 26			
All randomized patients	30.0% (51/170)	44.4% (75/169) ($p = 0.006$)*	56.8% (96/169) ($p < 0.001$)*

* P-values represent each infliximab treatment group vs. AZA monotherapy

Similar trends in the achievement of corticosteroid-free clinical remission were observed at Week 50. Furthermore, improved quality of life as measured by IBDQ was observed with infliximab.

Induction Treatment in Fistulizing Active Crohn's Disease
The efficacy was assessed in a randomized, double-blinded, placebo-controlled study in 94 adult patients with fistulizing Crohn's disease who had fistulae that were of at least 3 months' duration. Thirty-one of these patients were treated with infliximab 5 mg/kg. Approximately 93% of the patients had previously received antibiotic or immunosuppressive therapy.

Concurrent use of stable doses of conventional therapies was permitted, and 83% of patients continued to receive at least one of these medications. Patients received three doses of either placebo or infliximab at weeks 0, 2 and 6. Patients were followed up to 26 weeks. The primary endpoint was the proportion of patients who experienced a clinical response, defined as ≥ 50% reduction from baseline in the number of fistulae draining upon gentle compression

on at least two consecutive visits (4 weeks apart), without an increase in medication for Crohn's disease.

68% (21/31) of infliximab-treated patients receiving a 5 mg/kg dose regimen achieved a clinical response vs. 26% (8/31) placebo-treated patients (p = 0.002). The median time to onset of response in the infliximab-treated group was 2 weeks. The median duration of response was 12 weeks. Additionally, closure of all fistulae was achieved in 55% of infliximab-treated patients compared with 13% of placebo-treated patients (p = 0.001).

Maintenance Treatment in Fistulizing Active Crohn's Disease
The efficacy of repeated infusions with infliximab in patients with fistulizing Crohn's disease was studied in a 1-year clinical study. A total of 306 patients received 3 doses of infliximab 5 mg/kg at Week 0, 2 and 6. At baseline, 87% of the patients had perianal fistulae, 14% had abdominal fistulae, 9% had rectovaginal fistulae. The median CDAI score was 180. At Week 14, 282 patients were assessed for clinical response and randomized to receive either placebo or 5 mg/kg infliximab every 8 weeks through Week 46.

Week-14 responders (195/282) were analyzed for the primary endpoint, which was time from randomization to loss of response (see Table 7). Corticosteroid tapering was permitted after Week 6.

Table 7: Effects on Response Rate, Data from ACCENT II (Week-14 responders)

	ACCENT II (Week-14 responders)		
	Placebo Maintenance (n=99)	**Infliximab Maintenance (5 mg/kg) (n=96)**	**p-value**
Median time to loss of response through Week 54	14 weeks	> 40 weeks	< 0.001
Week 54			
Fistula response (%)[a]	23.5	46.2	0.001
Complete fistula response (%)[b]	19.4	36.3	0.009

[a]: A ≥50% reduction from baseline in the number of draining fistulas over a period of ≥4 weeks
[b]: Absence of any draining fistulas

Beginning at Week 22, patients who initially responded to treatment and subsequently lost their response were eligible to cross over to active re-treatment every 8 weeks at a dose of infliximab 5 mg/kg higher than the dose to which they were originally randomized. Among patients in the infliximab 5 mg/kg group who crossed over because of loss of fistula response after Week 22, 57% (12/21) responded to re-treatment with infliximab 10 mg/kg every 8 weeks.

There was no significant difference between placebo and infliximab for the proportion of patients with sustained closure of all fistulas through Week 54, for symptoms such as proctalgia, abscesses and urinary tract infection or for number of newly developed fistulas during treatment.

Maintenance therapy with infliximab every 8 weeks significantly reduced disease-related hospitalizations and surgeries compared with placebo. Furthermore, a reduction in corticosteroid use and improvements in quality of life were observed.

Pediatric Crohn's Disease (6 to 17 years)

In the REACH trial, 112 patients (6 to 17 years, median age 13.0 years) with moderate to severe, active Crohn's disease (median PCDAI of 40) and an inadequate response to conventional therapies were to receive 5 mg/kg infliximab at weeks 0, 2, and 6. All patients were required to be on a stable dose of 6-mercaptopurine (6-MP), azathioprine (AZA) or methotrexate (MTX) (35% were also receiving corticosteroids at baseline). Patients assessed by the investigator to be in clinical response at Week 10 were randomized and received 5 mg/kg infliximab either every 8-weeks or every 12-weeks as maintenance treatment regimen. If response was lost during treatment, crossing over to a higher dose (10 mg/kg) and/or shorter dosing interval (every 8-weeks) was allowed. 32 evaluable pediatric patients crossed over (9 subjects in the every 8-weeks and 23 subjects in the every 12-weeks maintenance groups). 24 of these patients (75.0%) regained clinical response after crossing over.

The proportion of subjects in clinical response at Week 10 was 88.4% (99/112). The proportion of subjects achieving clinical remission at Week 10 was 58.9% (66/112).

At Week 30, the proportion of subjects in clinical remission was higher in the every 8-week (59.6%, 31/52) than the every 12-week maintenance treatment group (35.3%, 18/51; $p = 0.013$) at Week 54, the figures were 55.8% (29/52) and 23.5% (12/51) in the every 8-weeks and every 12-weeks maintenance groups, respectively ($p < 0.001$).

Data about fistulas were derived from PCDAI scores. Of the 22 subjects that had fistulas at baseline, 63.6% (14/22), 59.1% (13/22) and 68.2% (15/22) were in complete fistula response at Week 10, 30 and 54, respectively, in the combined every 8-weeks and every 12-weeks maintenance groups.

In addition, statistically and clinically significant improvements in quality of life and height, as well as a significant reduction in corticosteroid use, were observed versus baseline.

Ulcerative Colitis

The safety and efficacy of infliximab was assessed in two (ACT 1 and ACT 2) randomized, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2) with an inadequate response to conventional therapies (oral corticosteroids, aminosalicylates and/or immunomodulators [6-MP, AZA]). Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. In both studies, patients were randomized to receive either placebo, 5 mg/kg infliximab, or 10 mg/kg infliximab at weeks 0, 2, 6, 14 and 22, and in ACT 1 at weeks 30, 38 and 46. Corticosteroid taper was permitted after Week 8.

Table 8: Effects on Clinical Response, Clinical Remission and Mucosal Healing at Weeks 8 and 30. Combined Data from ACT 1 & 2.

		Infliximab		
	Placebo	**5 mg/kg**	**10 mg/kg**	**Combined**
Subjects randomized	244	242	242	484
Percentage of subjects in clinical response and in sustained clinical response				
Clinical response at Week 8[a]	33.2%	66.9%	65.3%	66.1%

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Clinical response at Week 30[a]	27.9%	49.6%	55.4%	52.5%
Sustained response (clinical response at both Week 8 and Week 30)[a]	19.3%	45.0%	49.6%	47.3%
Percentage of subjects in clinical remission and sustained remission				
Clinical remission at Week 8[a]	10.2%	36.4%	29.8%	33.1%
Clinical remission at Week 30[a]	13.1%	29.8%	36.4%	33.1%
Sustained remission (in remission at both Week 8 and Week 30)[a]	5.3%	19.0%	24.4%	21.7%
Percentage of subjects with mucosal healing				
Mucosal healing at Week 8[a]	32.4%	61.2%	60.3%	60.7%
Mucosal healing at Week 30[a]	27.5%	48.3%	52.9%	50.6%

[a]: $p < 0.001$, for each infliximab treatment group vs. placebo

The efficacy of infliximab through Week 54 was assessed in the ACT 1 trial.

At 54 weeks, 44.9% of patients in the combined infliximab treatment group were in clinical response compared to 19.8% in the placebo treatment group ($p < 0.001$). Clinical remission and mucosal healing occurred in greater proportion of patients in the combined infliximab treatment group compared to the placebo treatment group at Week 54 (34.5% vs. 16.5%, $p < 0.001$ and 46.1% vs. 18.2%, $p < 0.001$, respectively). The proportions of patients in sustained response and sustained remission at Week 54 were greater in the combined infliximab treatment group than in placebo treatment group (37.9% vs. 14.0%, $p < 0.001$; and 20.2% vs. 6.6%, $p < 0.001$, respectively).

Infliximab improved quality of life, confirmed by statistically and clinically significant improvement in both disease specific measure, IBDQ, and by improvement in the generic 36-item short form survey SF-36.

From baseline through Week 30 in the pooled data from ACT 1 and ACT 2, the mean number of hospitalizations was 50% lower in the combined infliximab treatment group than in the placebo treatment group (9 vs. 18 hospitalizations per 100 subjects, $p = 0.005$). No notable differences were observed between the 5 mg/kg and 10 mg/kg infliximab treatment groups.

A greater proportion of adult patients in the combined infliximab treatment group were able to discontinue corticosteroids in clinical remission compared to the placebo treatment group at both Week 30 (22.3% vs. 7.2%, $p \leq 0.001$) and Week 54 (21.0% vs. 8.9%, $p = 0.022$).

Ulcerative Colitis in Pediatric Patients

The safety and efficacy of infliximab were assessed in a multicenter, randomized, open-label, parallel-group Phase 3 clinical study in 60 pediatric patients aged 6 through 17 years (median age 14.5 years) with moderately to severely active ulcerative colitis (Mayo score of 6 to 12; Endoscopic subscore ≥ 2) with an inadequate response to conventional therapies (Study Peds UC). At baseline 53% of patients were receiving immunomodulator therapy (6-mercaptopurine [6-MP]/ azathioprine [AZA]/ methotrexate [MTX]) and 62% of patients were receiving corticosteroids. Discontinuation of immunomodulators and corticosteroid taper were permitted after Week 0.

All patients received an induction regimen of 5 mg/kg infliximab at Weeks 0, 2, and 6. Patients (15) who did not respond to infliximab at Week 8 received no further drug and returned for safety follow-up. At Week 8, 45 patients were randomized in a 1:1 ratio to one of two maintenance treatment regimens: 5 mg/kg infliximab every 8 weeks (every 8-week) through Week 46 or every 12 weeks (every 12-week) through Week 42.

The primary endpoint was clinical response at Week 8, defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.

Major secondary endpoints included clinical remission measured by the Mayo score at Week 8, remission by the Pediatric Ulcerative Colitis Activity Index (PUCAI) score at Week 8 and Week 54, and mucosal healing at Week 8. For patients receiving corticosteroids at baseline, reduction in median corticosteroid use, and remission combined with elimination of corticosteroid use at Week 54 was evaluated.

Clinical Response, Clinical Remission and Mucosal Healing
Of the 60 patients treated, 44 (73.3%) were in clinical response at Week 8 (95% CI: 62.1%, 84.5%). The proportion of patients achieving clinical response at Week 8 was similar between those taking concomitant immunomodulators at baseline (72%) and those not taking concomitant immunomodulators at baseline (75%).

Clinical remission was defined by a Mayo score of ≤ 2 points, with no individual subscore > 1. Remission was also defined by a PUCAI score of < 10 points. At Week 8, infliximab induced clinical remission in 40% (24/60) of patients as measured by the Mayo score and in 33.3% (17/51) of patients as measured by the PUCAI score.

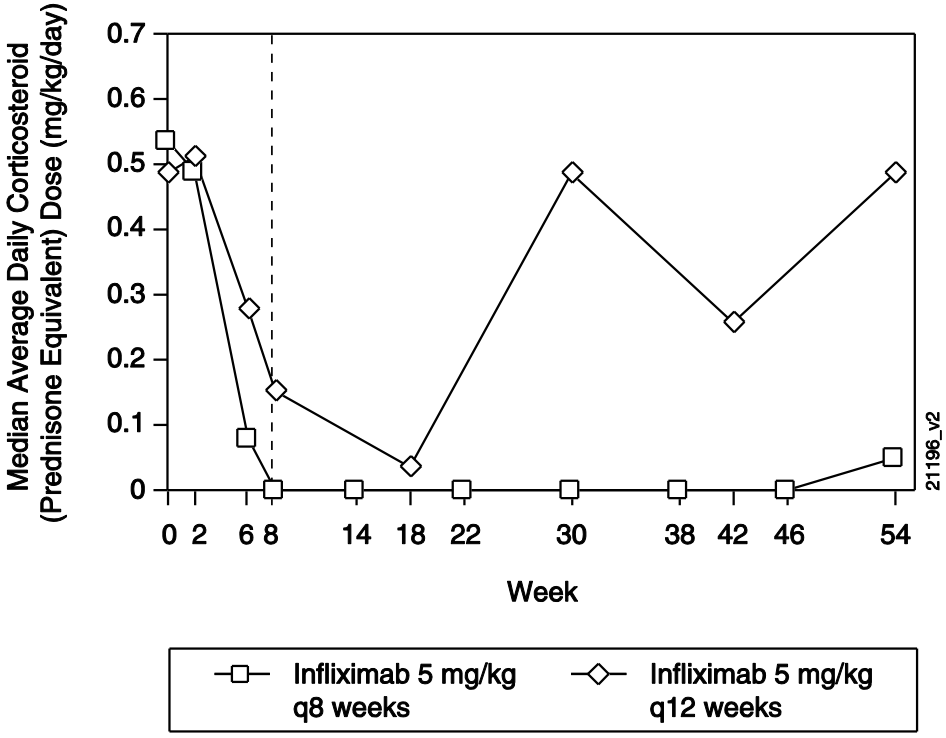
The proportion of patients in remission at Week 54 as measured by the PUCAI score was 38% (8/21) in the every 8-week maintenance treatment group and 18% (4/22) in the every 12-week maintenance treatment group.

Mucosal healing was defined as an endoscopy subscore (from the Mayo score) of 0 or 1. At Week 8, 68.3% (41/60) of patients were in mucosal healing with 33.3% (20/60) having an endoscopy subscore of 0 (indicating normal or inactive disease). Of the 9 patients who had an optional endoscopy at Week 54, 8 were in mucosal healing.

Overall, although some differences were noted between the age groups in the efficacy measures examined, efficacy was observed in both age groups and no consistent pattern indicating greater efficacy in one of the age groups was apparent. The differences between the 6 to 11 and the 12 to 17 year-old age groups, however, are difficult to assess because of the small sample sizes, particularly in the 6 to 11 year-old age group (15 patients).

Corticosteroid Use and Remission
Median average daily corticosteroid (prednisone equivalent) dose (mg/kg/day) through Week 54 is presented in Figure 1 for all randomized patients taking corticosteroids at baseline (14 patients in each maintenance treatment group).

Figure 1. Line plot of median average daily corticosteroid (prednisone equivalent) dose (mg/kg/day) through Week 54; randomized patients taking corticosteroids at baseline



At Week 54, the proportion of patients in clinical remission as measured by the PUCAI score was 38% (8/21) in the every 8-week maintenance group and 18% (4/22) in the every 12-week maintenance treatment group. For patients receiving corticosteroids at baseline, the proportion of patients in remission and not receiving corticosteroids at Week 54 was 38.5% (5/13) for the every 8-week and 0% (0/13) for the every 12-week maintenance treatment group.

For patients receiving corticosteroids at baseline in Study Peds UC, the proportion of these patients in remission and not receiving corticosteroids at Week 54 was 38.5% (5/13) for the every 8-week and 0% (0/13) for the every 12-week maintenance treatment group.

Ankylosing Spondylitis

Efficacy and safety were studied in a double-blind, placebo-controlled investigator-initiated, multicenter study evaluating infliximab in 70 patients with active ankylosing spondylitis (disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score > 4] and pain [NRS score > 4]). During the 3-month double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6 (35 patients in each group). Starting at Week 12, placebo patients were switched to infliximab and all patients subsequently received 5 mg/kg infliximab every 6 weeks up to Week 54.

Treatment with infliximab resulted in improvement in signs and symptoms, as assessed by the BASDAI, with 57% of infliximab-treated patients achieving at least 50% reduction from baseline in BASDAI score (mean baseline score was 6.5 in the infliximab group and 6.3 in the placebo group, compared with 9% of placebo patients ($p < 0.01$). Improvement was observed at Week 2 and was maintained through Week 54. Physical function and quality of

life (SF36) were improved similarly. In the trial, efficacy was not shown in HLA-B27 negative patients (n = 7).

Psoriatic Arthritis

Efficacy and safety were studied in a double-blind, placebo-controlled, multicenter study evaluating infliximab in 104 patients with active polyarticular psoriatic arthritis. In total 74 subjects were on at least one concomitant DMARD, and among those 58 patients were treated with methotrexate. During the 16-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6, and 14 (52 patients in each group). Starting at Week 16, placebo patients were switched to infliximab and all patients subsequently received 5 mg/kg infliximab every 8 weeks up to Week 46. After the first year of the study, 78 patients continued into an open-label extension to Week 98.

In the second trial (IMPACT 2), efficacy and safety of infliximab were studied in 200 patients with active psoriatic arthritis (≥ 5 swollen joints and ≥ 5 tender joints). 46% of patients continued on stable doses of methotrexate (≤ 25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6, 14, and 22 (100 patients in each group). At Week 16, 47 placebo patients with < 10% improvement from baseline in both swollen and tender joint counts were switched to infliximab induction (early escape). At Week 24, all placebo-treated patients crossed over to infliximab induction. Dosing continued for all patients through Week 46.

Key efficacy results for IMPACT and IMPACT 2 are shown in Table 9 below:

Table 9: Effects on ACR and PASI in IMPACT and IMPACT 2

	IMPACT			**IMPACT 2***		
	Placebo (Week 16)	**Infliximab (Week 16)**	**Infliximab (Week 98)**	**Placebo (Week 24)**	**Infliximab (Week 24)**	**Infliximab (Week 54)**
Patients randomized	52	52	N/A[a]	100	100	100
ACR response (% of patients)						
N	52	52	78	100	100	100
ACR 20 response*	5 (10%)	34 (65%)	48 (62%)	16 (16%)	54 (54%)	53 (53%)
ACR 50 response*	0 (0%)	24 (46%)	35 (45%)	4 (4%)	41 (41%)	33 (33%)
ACR 70 response*	0 (0%)	15 (29%)	27 (35%)	2 (2%)	27 (27%)	20 (20%)
PASI response (% of patients)[b]						
N				87	83	82
PASI 75 response**				1 (1%)	50 (60%)	40 (48.8%)

* ITT-analysis where subjects with missing data were included as non-responders

[a] Week 98 data for IMPACT includes combined placebo crossover and infliximab patients who entered the open-label extension

[b] Based on patients with PASI >2.5 at baseline for IMPACT, and patients with >3% BSA psoriasis skin involvement at baseline in IMPACT 2

** PASI 75 response for IMPACT not included due to low N; p<0.001 for infliximab vs. placebo at Week 24 for IMPACT 2

In IMPACT and IMPACT 2, clinical responses were observed as early as Week 2 and were maintained through Week 98 and Week 54 respectively. Efficacy has been demonstrated with or without concomitant use of methotrexate. Decreases in parameters of peripheral activity characteristic of psoriatic arthritis (such as number of swollen joints, number of painful/tender joints, dactylitis and presence of enthesopathy) were seen in the infliximab-treated patients.

Infliximab-treated patients demonstrated significant improvement in physical function as assessed by HAQ. Significant improvements in health-related quality of life were also demonstrated as measured by the physical and mental component summary scores of the SF-36 in IMPACT 2.

Psoriasis

The efficacy of infliximab was assessed in two multicenter, randomized, double-blind studies: SPIRIT and EXPRESS. Patients in both studies had plaque psoriasis (Body Surface Area [BSA] ≥ 10% and Psoriasis Area and Severity Index [PASI] score ≥ 12). The primary endpoint in both studies was the percent of patients who achieved ≥ 75% improvement in PASI from baseline at Week 10.

SPIRIT evaluated the efficacy of infliximab induction therapy in 249 patients with plaque psoriasis that had previously received PUVA or systemic therapy. Patients received either 3 or, 5 mg/kg infliximab or placebo infusions at weeks 0, 2 and 6. Patients with a PGA score ≥ 3 were eligible to receive an additional infusion of the same treatment at Week 26.

In SPIRIT, the proportion of patients achieving PASI 75 at Week 10 was 71.7% in the 3 mg/kg infliximab group, 87.9% in the 5 mg/kg infliximab group, and 5.9% in the placebo group ($p < 0.001$).

By Week 26, twenty weeks after the last induction dose, 30% of patients in the 5 mg/kg group and 13.8% of patients in the 3 mg/kg group were PASI 75 responders. Between weeks 6 and 26, symptoms of psoriasis gradually returned with a median time to disease relapse of > 20 weeks. No rebound was observed.

EXPRESS evaluated the efficacy of infliximab induction and maintenance therapy in 378 patients with plaque psoriasis. Patients received 5 mg/kg infliximab or placebo infusions at weeks 0, 2 and 6 followed by maintenance therapy every 8 weeks through Week 22 in the placebo group and through Week 46 in the infliximab group. At Week 24, the placebo group crossed over to infliximab induction therapy (5 mg/kg) followed by infliximab maintenance therapy (5 mg/kg). Nail psoriasis was assessed using the Nail Psoriasis Severity Index (NAPSI). Prior therapy with PUVA, methotrexate, cyclosporin, or acitretin had been received by 71.4% of patients, although they were not necessarily therapy resistant. Key results are presented in Table 10. In infliximab-treated subjects, significant PASI 50 responses were apparent at the first visit (Week 2) and PASI 75 responses by the second visit (Week 6). Efficacy was similar in the subgroup of patients that were exposed to previous systemic therapies compared to the overall study population.

Table 10: Summary of PASI Response, PGA Response and Percent of Patients with All Nails Cleared at Weeks 10, 24 and 50. EXPRESS

	Placebo → Infliximab 5 mg/kg (at Week 24)	**Infliximab 5 mg/kg**
Week 10		
N	77	301
≥ 90% improvement	1 (1.3%)	172 (57.1%)[a]
≥ 75% improvement	2 (2.6%)	242 (80.4%)[a]
≥ 50% improvement	6 (7.8%)	274 (91.0%)

PGA of cleared (0) or minimal (1)	3 (3.9%)	242 (82.9%)[ab]
PGA of cleared (0), minimal (1), or mild (2)	14 (18.2%)	275 (94.2%)[ab]
Week 24		
N	77	276
≥ 90% improvement	1 (1.3%)	161 (58.3%)[a]
≥ 75% improvement	3 (3.9%)	227 (82.2%)[a]
≥ 50% improvement	5 (6.5%)	248 (89.9%)
PGA of cleared (0) or minimal (1)	2 (2.6%)	203 (73.6%)[a]
PGA of cleared (0), minimal (1), or mild (2)	15 (19.5%)	246 (89.1%)[a]
Week 50		
N	68	281
≥ 90% improvement	34 (50.0%)	127 (45.2%)
≥ 75% improvement	52 (76.5%)	170 (60.5%)
≥ 50% improvement	61 (89.7%)	193 (68.7%)
PGA of cleared (0) or minimal (1)	46 (67.6%)	149 (53.0%)
PGA of cleared (0), minimal (1), or mild (2)	59 (86.8%)	189 (67.3%)
All nails cleared[c]		
Week 10	1/65(1.5%)	16/235 (6.8%)
Week 24	3/65 (4.6%)	58/223 (26,0%)[a]
Week 50	27/64 (42.2%)	92/226 (40.7%)

[a]: $p < 0.001$, for each infliximab treatment group vs. control
[b]: n = 292
[c]: Analysis was based on subjects with nail psoriasis at baseline (81.8% of subjects). Mean baseline NAPSI scores were 4.6 and 4.3 in infliximab and placebo group.

Significant improvements from baseline were demonstrated in DLQI ($p < 0.001$) and the physical and mental component scores of the SF 36 ($p < 0.001$ for each component comparison).

IXIFI Clinical Study - Rheumatoid Arthritis

The biosimilar clinical development program for IXIFI included a randomized, double-blind, active-controlled trial in subjects with moderately to severely active RA who have had an inadequate response to background MTX.

Study B5371002 was a multi-national, double-blind, randomized, comparative efficacy and safety study of 650 subjects designed to demonstrate the absence of clinically meaningful differences in the efficacy, safety and immunogenicity of IXIFI and the reference product (Remicade, sourced from the EU), and to evaluate the safety and immunogenicity of IXIFI after treatment transition from Remicade to IXIFI. The same dose regimen was followed for 3 mg/kg at Weeks 0, 2, and 6, followed by a maintenance regimen of every 8 weeks, with a one-time escalation to 5 mg/kg occurring on or after Week 14 for insufficient efficacy. The primary efficacy endpoint was ACR20 response rate at Week 14. Secondary endpoints included the ACR20 time course to Week 30, ACR50/70, DAS28-CRP, European League Against Rheumatism (EULAR) response, and ACR/EULAR remission evaluations. At Week 30, 50% of the Remicade arm were blindly re-randomized to the IXIFI arm. At Week 54, all patients received open label IXIFI for an additional 24 weeks.

For the ACR20 primary endpoint at Week 14, response rates were 62.7% for IXIFI and 64.1% for Remicade. In both ITT and PP populations, the 2-sided 95% CIs and 90% CIs of the treatment difference in Week 14 ACR20 response rate between the 2 groups were entirely contained within a symmetric equivalence margin of (-13.5% to 13.5%), and an asymmetric

equivalence margin of (-12% to 15%), demonstrating therapeutic equivalence (similarity) between IXIFI and Remicade treatments.

Similar responses between IXIFI and Remicade treatments were observed at each study visit up to Week 30 as measured by ACR20, ACR50, ACR70, individual ACR parameters (including HAQ-DI), DAS28-CRP, EULAR response, DAS remission and ACR/EULAR remission. No clinically meaningful differences in safety or immunogenicity were found between IXIFI and Remicade.

In line with the findings from the first treatment period, results from the second period with dosing up to Week 54 continued to show the absence of clinically meaningful differences in efficacy, PD, immunogenicity and safety among subjects receiving IXIFI, Remicade, and subjects who transitioned from Remicade to IXIFI.

Overall, in line with the findings from the first 2 treatment periods, results from the third treatment period (final period; from Week 54 to Week 78) supported the efficacy and safety of IXIFI in subjects with moderately to severely active RA who were treated with IXIFI in combination with methotrexate. Furthermore, results from the final period showed the absence of clinically meaningful differences in efficacy, PK, PD, immunogenicity and safety among the three treatment groups in the final period independent of single treatment transition from Remicade to IXIFI at Week 30 or Week 54.

Based on the comparative clinical efficacy and safety results obtained in Study B5371002 in subjects with RA, it is concluded that biosimilarity was demonstrated between IXIFI and Remicade. The totality of evidence supports that IXIFI is biosimilar to Remicade.

5.2. Pharmacokinetic properties

Adults

Single intravenous infusions of 1, 3, 5, 10 or 20 mg/kg of infliximab yielded dose proportional increases in the maximum serum concentration (C_{max}) and area under the concentration-time curve (AUC). The volume of distribution at steady state (median V_d of 3.0 to 4.1 liters) was not dependent on the administered dose and indicated that infliximab is predominantly distributed within the vascular compartment. No time-dependency of the pharmacokinetics was observed. The elimination pathways for infliximab have not been characterized. Unchanged infliximab was not detected in urine. No major age- or weight-related differences in clearance or volume of distribution were observed in rheumatoid arthritis patients. The pharmacokinetics of infliximab in elderly patients has not been studied. Studies have not been performed in patients with liver or renal disease.

At single doses of 3, 5, or 10 mg/kg, the median C_{max} values were 77, 118 and 277 micrograms/mL, respectively. The median terminal half-life at these doses ranged from 8 to 9.5 days. In most patients, infliximab could be detected in the serum for at least 8 weeks after the recommended single dose of 5 mg/kg for Crohn's disease and the rheumatoid arthritis maintenance dose of 3 mg/kg every 8 weeks.

Repeated administration of infliximab (5 mg/kg at 0, 2 and 6 weeks in fistulizing Crohn's disease, 3 or 10 mg/kg every 4 or 8 weeks in rheumatoid arthritis) resulted in a slight accumulation of infliximab in serum after the second dose. No further clinically relevant

accumulation was observed. In most fistulizing Crohn's disease patients, infliximab was detected in serum for 12 weeks (range 4-28 weeks) after administration of the regimen.

Pediatrics

Infliximab pharmacokinetic characteristics (including peak and trough concentrations and terminal half-life) were generally similar in pediatric (aged 6 to 17 years) and adult patients with Crohn's disease or ulcerative colitis following the administration of 5 mg/kg infliximab.

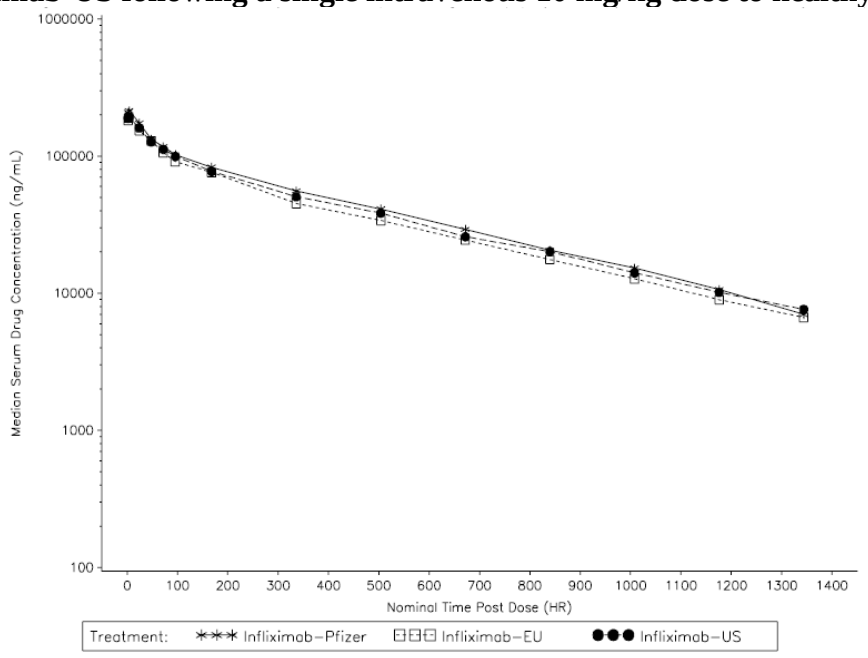
Population pharmacokinetic analysis based on data obtained from patients with ulcerative colitis (N = 60), Crohn's disease (N = 112), juvenile rheumatoid arthritis (N = 117) and Kawasaki disease (N = 16) with an overall age range from 2 months to 17 years indicated that the total clearance of infliximab did not increase linearly with increasing body weight. As a result, following administration of 5 mg/kg infliximab every 8 weeks, the predicted median steady-state infliximab exposure (area under concentration-time curve at steady state, AUC_{ss}) in pediatric patients aged 6 to 17 years was approximately 20% lower than the median steady-state drug exposure in adults. The median AUC_{ss} in pediatric patients aged 2 to less than 6 years was predicted to be approximately 40% lower than that in adults, although the number of patients supporting this estimate is limited.

IXIFI Comparative Pharmacokinetic Studies

The PK similarity of IXIFI and Remicade was evaluated in the clinical development program. Study B5371001 was a three-arm, double-blind, randomized (1:1:1), parallel-group, single-dose study that compared the PK of IXIFI, infliximab-EU and infliximab-US following IV administration of 10 mg/kg to healthy adult subjects.

The 3 study drugs exhibited a similar median PK profile, which was characterized by a rapid increase of serum drug concentrations during each infusion, followed by a multi-phasic decline in drug concentrations after completion of the IV infusion.

Figure 2. Median serum concentration-time profiles of IXIFI, Infliximab-EU, and Infliximab-US following a single intravenous 10 mg/kg dose to healthy subjects



The arithmetic mean (±SD) PK parameters for IXIFI, infliximab-EU, and infliximab-US are summarized in Table 11. Consistent with the concentration-time profiles, the mean C_{max}, AUC_T and AUC_{inf} estimates were similar among the 3 study drugs. In addition, the inter-subject variability for each of the PK parameters was similar across the 3 study drugs, with %CV values of 20% to 24%, 21% to 25%, and 23% to 28% for C_{max}, AUC_T and $AUC_{inf,}$ respectively.

Table 11: Arithmetic Mean (±SD) Pharmacokinetic Parameter Estimates of IXIFI, Infliximab-EU, and Infliximab-US: Per-protocol Analysis Set

Parameters (units)	IXIFI	Infliximab-EU	Infliximab-US
N, n	41, 41	45, 45	44, 44
C_{max} (µg/mL)	221.9 ± 43.8	202.7 ± 46.1	209.3 ± 50.5
AUC_T[a] (µg•hr/mL)	56960 ± 12157	51180 ± 12868	53010 ± 11906
AUC_{inf} (µg•hr/mL)	61460 ± 14386	56130 ± 15972	57610 ± 14334
CL (mL/hr/kg)	0.1725 ± 0.0456	0.1918 ± 0.0527	0.1855 ± 0.0521
V_{ss} (mL/kg)	79.58 ± 20.73	92.06 ± 25.85	84.92 ± 24.52
$t_{½}$ (hr)	344.5 ± 99.72	367.6 ± 106.7	335.1 ± 124.5

Abbreviations: EU = European Union; hr = hour(s); N = number of subjects included for PK analysis in the treatment group; n = number of subjects with reportable AUC_{inf}, CL, V_{ss} and $t_{½}$ values; PK = pharmacokinetic(s); SD = standard deviation; US = United States.

a. AUC_T was ≥ 80% of the corresponding AUC_{inf} in 127 of 130 subjects who were included for PK analysis.

The 90% CIs for test-to-reference ratios of C_{max}, AUC_t, and AUC_{inf} were all contained within the pre-specified acceptance boundaries of 80.00% to 125.00% for the comparisons of IXIFI to infliximab-US, IXIFI to infliximab-EU, and infliximab-EU to infliximab-US. This study demonstrated the PK similarity of IXIFI to both infliximab-US and infliximab-EU, and of infliximab-EU to infliximab-US.

Table 12: Summary of Statistical Comparisons of Pharmacokinetic Exposure Parameters (C_{max}, AUC_T, and AUC_{inf}) between Test and Reference Products: Per-protocol Analysis Set

	Adjusted Geometric Means		Ratios (Test/Reference) of Adjusted	
Parameters (units)	Test	Reference	Geometric Means[a]	90% CIs for Ratios
IXIFI (Test) vs. Infliximab-EU (Reference)				
C_{max} (µg/mL)	217.4	197.6	110.03	101.32 – 119.49
AUC_T (µg•hr/mL)	55600	49650	111.98	102.85 – 121.92
AUC_{inf} (µg•hr/mL)	59750	54080	110.49	100.67 – 121.28
IXIFI (Test) vs. Infliximab-US (Reference)				
C_{max} (µg/mL)	217.4	203.1	107.05	98.53 – 116.31
AUC_T (µg•hr/mL)	55600	51640	107.67	98.85 – 117.28
AUC_{inf} (µg•hr/mL)	59750	55810	107.06	97.49 – 117.58
Infliximab-EU (Test) vs. Infliximab-US (Reference)				
C_{max} (µg/mL)	197.6	203.1	97.29	89.72 – 105.50
AUC_T (µg•hr/mL)	49650	51640	96.15	88.45 – 104.53
AUC_{inf} (µg•hr/mL)	54080	55810	96.90	88.42 – 106.18

Pharmacokinetic parameters are defined in Study B5371001 CSR, Table 1.

Abbreviations: CI = confidence interval; EU = European Union; hr = hour(s); US = United States.

a. The ratios (and 90% CIs) are expressed as percentages.

In Study B5371002, the median C_{trough} and C_{max} values, as well as the corresponding ranges, were similar between the IXIFI and infliximab-EU arms. The concentrations of serum IXIFI

and infliximab-EU were lower in ADA-positive subjects compared to ADA-negative subjects. The effect of ADA on PK in ADA-positive subjects was similar between treatment arms in all three treatment periods.

Table 13: Serum IXIFI and Infliximab-EU Concentrations, PK population – Treatment Period 1

	All Subjects		ADA-Positive Subjects		ADA-Negative Subjects	
Visit	**IXIFI**	**Infliximab-EU**	**IXIFI**	**Infliximab-EU**	**IXIFI**	**Infliximab-EU**
C_{trough} (ng/mL)						
Week 0 (Day 1)	N = 322 0 (0-0)	N = 323 0 (0-0)	N = 156 0 (0-0)	N = 166 0 (0-0)	N = 163 0 (0-0)	N = 156 0 (0-0)
Week 2	N = 316 16830 (6241-28660)	N = 323 16070 (6241-27270)	N = 155 15540 (5675-26780)	N = 166 14230 (5243-26130)	N = 161 18230 (6316-28830)	N = 157 18020 (9075-29630)
Week 4	N = 308 23540 (4300-45750)	N = 314 21250 (2258-40120)	N = 151 17760 (765-37420)	N = 164 16370 (256-32450)	N = 157 27850 (10660-49180)	N = 150 26880 (12980-41390)
Week 6	N = 308 10020 (102-26650)	N = 315 9266 (0-24180)	N = 151 6159 (0-20180)	N = 163 5122 (0-17440)	N = 157 14030 (3960-29890)	N = 152 12790 (4321-26420)
Week 14	N = 302 1497 (0-10590)	N = 310 1025 (0-7643)	N = 154 0 (0-4014)	N = 159 0 (0-3428)	N = 148 3351 (492-15660)	N = 151 3063 (197-8440)
Week 22	N = 295 576 (0-7911)	N = 303 433 (0-6221)	N = 152 0 (0-2262)	N = 156 0 (0-1151)	N = 143 2977 (206-10640)	N = 147 2489 (0-7577)
Week 30	N = 281 413 (0-7253)	N = 290 279 (0-6017)	N = 143 0 (0-533)	N = 149 0 (0-575)	N = 138 2846 (386-10050)	N = 141 2385 (192-7580)
C_{max} (ng/mL)						
Week 0 (Day 1)	N = 319 64240 (31570-102000)	N = 322 62200 (23260-95990)	N = 154 63830 (35630-101500)	N = 166 59290 (1603-93170)	N = 162 65530 (11180-102000)	N = 155 66080 (29140-101200)
Week 14	N = 297 71250 (1617-150500)	N = 299 68450 (3367-144500)	N = 149 68280 (0-157500)	N = 152 62010 (1091-118200)	N = 148 75640 (5633-129400)	N = 147 75090 (8857-159800)

Data presented as median (5^{th} - 95^{th} percentile).
Abbreviations: ADA = anti-drug antibody; C_{max} = Observed serum drug concentration prior to the end of infusion; C_{trough} = observed pre-dose trough serum drug concentration; EU = European Union; N = number of observations; PK = Pharmacokinetics; SD = standard deviation.

Additionally, a population PK analysis did not reveal any appreciable differences between the PK of infliximab-EU and IXIFI in the RA patient population. This analysis identified covariates of body weight, sex and ADA titers as significant factors influencing infliximab-EU and IXIFI PK. Furthermore, results indicate that the PK of IXIFI was not different between Japanese and non-Japanese patients.

In conclusion, the PK results obtained in Studies B5371001 and B5371002 in healthy subjects and in subjects with RA, respectively, demonstrate PK similarity between IXIFI, infliximab-US, and infliximab-EU.

5.3. Preclinical safety data

Conventional preclinical safety data with infliximab is limited. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. In a fertility and general reproductive function study, the number of pregnant mice was reduced following administration of the same analogous antibody. It is not known whether this finding was due to effects on the males and / or the females. In a 6-month repeated dose toxicity study in mice, using the same analogous antibody against mouse TNFα, crystalline deposits were observed on the lens capsule of some of the treated male mice. No specific ophthalmologic examinations have been performed in patients to investigate the relevance of this finding for humans.

A 6-month study in CD-1 mice was conducted to assess the tumorigenic potential of cV1q anti-mouse TNFα, an analogous antibody. No evidence of tumorigenicity was observed in mice that received intravenous doses of 10 mg/kg or 40 mg/kg cV1q given weekly. The relevance of this study for human risk is unknown.

Long-term studies have not been performed to evaluate the carcinogenic potential of infliximab. Studies in mice deficient in TNFα demonstrated no increase in tumors when challenged with known tumor initiators and/or promoters.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Disodium succinate hexahydrate
Polysorbate 80
Succinic acid
Sucrose

6.2. Incompatibilities

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

6.3. Shelf life

Refer to Outer Carton.

6.4. Special precautions for storage

Store unopened IXIFI vials in a refrigerator at 2°C to 8°C. Do not use IXIFI beyond the expiration date located on the carton and the vial. This product contains no preservative.

Unopened IXIFI vials may also be stored at temperatures up to a maximum of 30°C for a single period of up to 6 months but not exceeding the original expiration date. The new expiration date must be written on the carton. Upon removal from refrigerated storage, IXIFI cannot be returned to refrigerated storage.

For storage conditions of the reconstituted product, see Section 6.6.

6.5. Nature and contents of container

One 15 mL Type I glass vial with chlorobutyl stopper and an aluminium crimp seal with a polypropylene flip-off cap.

Each IXIFI 15 mL vial is individually packaged in a carton.
Each single-dose vial contains 100 mg of infliximab for final reconstitution volume of 10 mL.

6.6. Special precautions for disposal and other handling

Reconstitution, Dilution and Administration Instructions

IXIFI is intended for use under the guidance and supervision of a healthcare provider. The supplied lyophilized power must be reconstituted and diluted prior to administration. The infusion solution should be prepared and administered by a trained medical professional using aseptic technique by the following procedure:

1. Calculate the dose, total volume of reconstituted IXIFI solution required and the number of IXIFI vials needed. More than one vial may be needed for a full dose.

2. Reconstitute each 100 mg IXIFI vial with 10 mL of Sterile Water for Injection, to obtain a concentration of 10 mg/mL, 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, to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder, which has a cake like appearance. 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. Visually inspect the reconstituted solution for particulate matter and discoloration. The reconstituted solution concentration is approximately 10 mg/mL. The solution should be colorless to light yellow or light brown and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if the lyophilized powder has not fully dissolved or if opaque particles, discoloration, or other foreign particles are present. Following reconstitution with 10 mL of Sterile Water for Injection, the resulting pH is approximately 6. Do not store unused reconstituted IXIFI solution.

3. Dilute the total volume of the reconstituted IXIFI solution to 250 mL* with sterile 0.9% Sodium Chloride Injection, (do not dilute with any other diluent) as follows:

- Withdraw a volume from the 0.9% Sodium Chloride Injection, 250 mL bottle or bag equal to the total volume of reconstituted IXIFI required for a dose. Slowly add the total volume of reconstituted IXIFI solution from the vial(s) to the 250 mL infusion bottle or bag.
- Discard any unused portion of the reconstituted IXIFI solution remaining in the vial(s).
- Gently invert the bag to mix the solution. The resulting infusion concentration should range between 0.4 mg/mL (minimum recommended concentration) and 4 mg/mL (maximum recommended concentration) of infliximab.

*For volumes greater than 250 mL, either use a larger infusion bag (e.g., 500 mL) or multiple 250 mL infusion bags to ensure that the concentration of the infusion solution does not exceed 4 mg/mL.

4. The IXIFI infusion should begin within 3 hours of reconstitution and dilution. The infusion must be administered intravenously for at least 2 hours with an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less).

5. Given that the vials do not contain antibacterial preservatives, discard any unused portion of the infusion solution (do not be store for reuse).

6. Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

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