AUSTRALIAN PRODUCT INFORMATION – IXIFI® (INFLIXIMAB)

1. NAME OF THE MEDICINE

IXIFI® 100 mg lyophilised powder for injection.

IXIFI is a biosimilar medicine to Remicade®. The evidence for comparability supports the use of IXIFI for the listed indications.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains infliximab 100 mg Powder for Injection. After reconstitution, each mL contains 10 mg of infliximab.

Each vial of IXIFI contains 100 mg of infliximab, a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology.

IXIFI Powder for Injection is to be reconstituted with sterile Water for Injections and further diluted in 0.9% sodium chloride solution for infusion. After reconstitution, each vial of IXIFI contains infliximab 100 mg/10 mL.

Excipient(s) with known effect

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Powder for injection.

IXIFI is supplied as a sterile white lyophilised powder in single-use glass vials with rubber stoppers and aluminium crimps protected by plastic caps. Vial stopper is free of natural rubber latex.

IXIFI Powder for Injection is to be reconstituted with 10 mL sterile Water for Injections and further diluted in 0.9% sodium chloride solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid Arthritis in adults

IXIFI, in combination with methotrexate, is indicated for the reduction of signs and symptoms and prevention of structural joint damage (erosions and joint space narrowing) in:

- patients with active disease despite treatment with methotrexate

- patients with active disease who have not previously received methotrexate.

IXIFI should be given in combination with methotrexate. Efficacy and safety in Rheumatoid Arthritis have been demonstrated only in combination with methotrexate.

Ankylosing Spondylitis

IXIFI is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease.

Psoriatic arthritis

IXIFI is indicated for the treatment of the signs and symptoms, as well as for the improvement in physical function in adult patients with active and progressive psoriatic arthritis who have responded inadequately to disease-modifying anti-rheumatic drug (DMARD) therapy.

IXIFI may be administered in combination with methotrexate.

Psoriasis

IXIFI is indicated for the treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate. Safety and efficacy beyond 12 months have not been established.

Crohn's Disease in Adults and in Children and adolescents (6 to 17 years)

IXIFI is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies.

Refractory Fistulising Crohn's Disease

IXIFI is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.

Ulcerative colitis in Adults and in Children and adolescents (6 to 17 years)

IXIFI is indicated for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy.

4.2 Dose and method of administration

Dosage

IXIFI is administered by intravenous infusion.

IXIFI is for intravenous use in adults across all indications. IXIFI is approved for intravenous use in children and adolescents (6 to 17 years) for the indication of Crohn's disease and ulcerative colitis.

IXIFI treatment is to be administered under the supervision of specialised physicians experienced in the diagnosis and treatment of rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel diseases, psoriasis or psoriatic arthritis.

For adult and paediatric patients, administer the infusion solution over a period of not less than

2 hours.

All patients administered IXIFI are to be observed for at least 1-2 hours post infusion for side effects. Medications, an artificial airway and other appropriate materials must be available for the treatment of these effects (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Shortened Infusions 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 time, then a slower infusion rate should be considered for future infusions if treatment is to be continued. For doses greater than 6mg/kg, data only support administering an infusion over a period of not less than two hours.

Rheumatoid Arthritis in adults

Patients not previously treated with IXIFI: Initially 3 mg/kg intravenous infusion is to be followed with additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

IXIFI should be given in combination with methotrexate.

To optimise clinical response, consideration may be given to adjusting the dose in increments of 1.5 mg/kg up to a maximum of 7.5 mg/kg.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. If a patient has an inadequate response or loses response after this period, the dose may be adjusted as described above. If adequate response is achieved, patients should be continued on the selected dose or dose frequency.

Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment or after dose adjustment.

Ankylosing Spondylitis

5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 weeks thereafter.

Psoriatic Arthritis

5 mg/kg given as an intravenous infusion 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 alone or in combination with methotrexate.

Psoriasis

5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusions doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Crohn's Disease

Moderate to severe Crohn's disease in adults and in children and adolescents (6 to 17 years)

For optimal long-term symptom control, 5 mg/kg given as a single intravenous infusion as an

induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter. For patients who have an incomplete response during maintenance treatment, consideration may be given to adjusting the dose up to 10 mg/kg.

Paediatric 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.

Available data do not support further infliximab treatment in children and adolescent patients (6-17 years) not responding within 10 weeks to the initial infusion.

Refractory Fistulising Crohn's disease

5 mg/kg given as a single intravenous infusion as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter. If a patient does not respond after the initial 3 dose induction regimen, no additional treatment with infliximab should be given.

For patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg.

There are no efficacy and safety data on the use of infliximab for the treatment of refractory fistulising Crohn's disease beyond 54 weeks.

Ulcerative colitis in adults and in children and adolescents (6 to 17 years)

5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion dose at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

If patients have not responded to the initial three treatment infusion regimen at weeks 0, 2, and 6 weeks, then careful consideration should be given before persisting with further treatment.

Available data do not support further infliximab treatment in children and adolescent patients (6-17 years) not responding within 8 weeks to the initial infusion.

Readministration

Readminstration for Crohn's disease, refractory fistulising Crohn's disease and Rheumatoid Arthritis

Readministration of a liquid formulation of infliximab, which is no longer in use, with a drug-free interval of 2 to 4 years following a previous infusion has been associated with a delayed hypersensitivity reaction in 10 patients with Crohn's disease (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE; Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). After a drug free interval of 16 weeks to 2 years, the risk of delayed hypersensitivity following readministration is not known. Therefore, after a drug free interval of 16 weeks, readministration is not recommended.

Readministration for Ankylosing Spondylitis

Data supporting readministration, other than every 6 weeks, are not available at this time (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Readministration for Psoriatic Arthritis

Data supporting readministration, other than every 8 weeks, are not available at this time (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Readministration for Psoriasis

Experience from intermittent treatment with IXIFI in psoriasis after a period of no treatment suggests reduced efficacy and a higher incidence of infusion reactions when compared to the approved dosing guidance (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Readministration for ulcerative colitis

Data supporting readministration, other than every 8 weeks, are not available at this time (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Preparation and administration

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 intravenous line with other agents.

The diluent to be used for reconstitution is 10 mL of Sterile Water for Injection. The total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection. The infusion concentration should range between 0.4 mg/mL and 4 mg/mL.

Since no preservative is present, it is recommended that the IXIFI infusion be started within 3 hours of reconstitution and dilution.

1) Under aseptic conditions, reconstitute each IXIFI vial with 10 mL of Sterile Water for Injection, using a syringe equipped with a 21-gauge or smaller needle. Upon reconstitution, each mL of reconstituted solution contains 10 mg of infliximab. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the centre of the rubber stopper and direct the stream of Sterile Water for Injection to the glass wall of the vial. Foaming of the solution on reconstitution is not unusual. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Gently swirl the solution by rotating the vial until the lyophilised cake is completely dissolved. Allow the reconstituted solution to stand for 5 minutes. Because IXIFI is a protein, the solution may develop a few fine translucent particles that do not affect its potency. The solution should be colourless to light yellow or light brown and opalescent. Do not use if opaque particles, discolouration, or other foreign particles are present. After reconstitution, the vials should be used immediately.

2) Further dilute the total volume of the reconstituted IXIFI solution dose to 250 mL with 0.9% Sodium Chloride Injection, by withdrawing a volume of 0.9% Sodium Chloride Injection, equal to the volume of reconstituted IXIFI from the 0.9% Sodium Chloride Injection, 250 mL bottle or bag. Do not dilute the reconstituted IXIFI solution with any other diluent. Slowly add the total volume of reconstituted IXIFI solution to the 250 mL infusion bottle or bag. Gently mix. Depending on the number of IXIFI vials used, the final concentration may range from 0.4 mg/mL to 4 mg/mL. For volumes greater than 250 mL,

either use a larger infusion bag (e.g. 500 mL, 1000 mL) or use multiple 250 mL infusion bags to ensure that the concentration of the infusion solution does not exceed 4 mg/mL.

3) Administer the infusion solution over a period of not less than the infusion time recommended for the specific indication – See Section 4.2 DOSE AND METHOD OF ADMINSTRATION. Use only an infusion set with an in-line, sterile, nonpyrogenic, low protein-binding filter (pore size 1.2 μm or less).

4) Visually inspect parenteral medicinal products for particulate matter or discolouration prior to administration. Do not use if visibly opaque particles, discolouration or foreign particulates are observed.

Reconstituted Solution

The IXIFI reconstituted vial is biochemically and microbiologically stable for 18 hours at ambient temperatures (up to 30°C). However, since no preservative is present and to reduce microbiological hazard, use as soon as practicable after reconstitution.

Diluted Solution for Infusion

IXIFI infusion solution diluted in 0.9% sodium chloride is biochemically and microbiologically stable for 24 hours when stored between 2°C and 30°C, however, since no preservative is present, and to reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2-8°C for not more than 24 hours.

The product is for single use only and any unused portion of the solution should be discarded.

Traceability

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

4.3 Contraindications

IXIFI is contraindicated in patients with severe infections such as sepsis, abscesses, tuberculosis and opportunistic infections.

IXIFI should not be given to patients with a history of hypersensitivity to infliximab (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) to other murine proteins or to any excipient of the product.

Concurrent administration of IXIFI and anakinra (an interleukin-1 receptor antagonist) is contraindicated.

Do not initiate therapy in patients with congestive heart failure.

4.4 Special warnings and precautions for use

Risk of Infections

Bacterial (including sepsis and pneumonia), mycobacterial [including tuberculosis (frequently

disseminated or extrapulmonary at clinical presentation)], invasive fungal, viral, and other opportunistic infections have been observed in patients receiving infliximab. Some of these infections have been fatal.

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

In clinical studies in rheumatoid arthritis, starting infliximab therapy with doses higher than 3 mg/kg has been associated with an increased risk of infection compared to the risk of infection associated with the starting dose of 3 mg/kg. This increase in the risk of infection was not evident in patients receiving the starting regimen of 3 mg/kg at weeks 0, 2 and 6 and subsequently receiving higher or more frequent doses. However, caution should be exercised when continuing a rheumatoid arthritis patient on doses above 3 mg/kg or administering infliximab more frequently than every 8 weeks.

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

Opportunistic infections including tuberculosis, viral infections, invasive fungal infections and other serious infections including sepsis and pneumonia have been reported in patients treated with infliximab (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Serious infections, including sepsis and fatal infections, have been reported in patients receiving TNF-blocking agents. Many of the serious infections in patients treated with infliximab have occurred in patients on concomitant immunosuppressive therapy that, in addition to their Crohn's disease or rheumatoid arthritis, could predispose them to infections.

Patients who have clinically manifested infections and/or abscesses must be treated for these conditions prior to treatment with infliximab as infliximab should not be given to patients with a clinically important, active infection.

Tuberculosis

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), has been observed in patients receiving infliximab. Patients must be evaluated for the risk of tuberculosis (including close contact with a person with active tuberculosis) and tested for latent tuberculosis, prior to initiation of infliximab. 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. 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, infliximab therapy must not be initiated (see Section 4.3 CONTRAINDICATIONS). If latent tuberculosis is diagnosed, treatment must be initiated prior to treatment with infliximab, in accordance with local recommendations. Use of anti-tuberculosis therapy should also be considered before the initiation of infliximab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients must be monitored closely for

infections, including miliary tuberculosis, while on and after treatment with infliximab.

Use of anti-tuberculosis therapy should be considered before the initiation of infliximab 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. Patients receiving infliximab should be monitored closely for signs and symptoms of active tuberculosis during and after treatment, including patients who tested negative for latent tuberculosis. 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 infliximab treatment.

Invasive Fungal Infections

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

In patients treated with infliximab, 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 anti-fungal therapy.

Other infections

Invasive fungal infections and other opportunistic infections have been observed in patients receiving infliximab. Caution should be exercised when considering the use of infliximab in patients with a chronic infection or a history of recurrent infection. Patients must be monitored closely for infections while on and after treatment with infliximab. Suppression of TNFα may also mask symptoms of infection such as fever. Patients who develop a serious new infection while undergoing treatment with infliximab should be treated for the infection as quickly as possible and monitored closely. During treatment with infliximab patients should be carefully monitored for respiratory tract and urinary tract infections. Treatment with infliximab must be discontinued if a patient develops a serious infection or sepsis. As the elimination of infliximab may take up to six months, a close monitoring of the patients throughout this period is important.

The use of TNFα blocking agents in patients with chronic viral infections such as HIV, Hepatitis B or C has not been studied. Therefore, infliximab should not be given to these patients.

Patients with fistulising Crohn's disease with acute suppurative fistulas should not initiate infliximab therapy until a source for possible infection, specifically abscess, has been excluded (see Section 4.3 CONTRAINDICATIONS).

There is limited safety experience of surgical procedures in infliximab-treated patients. A patient who requires surgery while on infliximab should be closely monitored for infections, and appropriate actions should be taken.

Use in patients with congestive heart failure

Do not initiate therapy in patients with congestive heart failure (see Section 4.3 CONTRAINDICATIONS).

Treatment should be discontinued in patients whose congestive heart failure is worsening.

Treatment discontinuation should be considered in patients with stable congestive heart failure, especially in those who have not had a significant clinical response to infliximab therapy. If a decision is made to continue treatment, cardiac status should be closely monitored and only the lower doses of infliximab should be considered (see Section 4.2 DOSAGE AND METHOD OF ADMINISTRATION and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Heart failure).

Infusion reactions and hypersensitivity reactions

Infliximab has been associated with acute infusion effects and a delayed hypersensitivity reaction. These differ in their time of onset. Hypersensitivity reactions, which include urticaria, dyspnoea, and/or bronchospasm, laryngeal oedema, pharyngeal oedema, and hypotension, have occurred during or within 2 hours of IXIFI infusion. Therefore, all patients receiving infliximab should be observed for at least one to two hours post infusion for side effects.

To minimise the incidence of hypersensitivity reactions, including infusion reactions and serum sickness-like reactions, infliximab should be administered as regular maintenance therapy after an induction regimen at weeks 0, 2, 6 (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Acute infusion reactions may develop immediately or within a few hours of infusion and are most likely to occur during the first and second infusion. These effects may be related to the rate of infusion of infliximab. If acute infusion reactions occur, the infusion must be interrupted immediately. Some of these effects have been described as anaphylaxis. Medications (e.g. antihistamines, corticosteroids, adrenaline and/or paracetamol), an artificial airway and other appropriate materials for the treatment of these effects must be available for immediate use. Patients may be pretreated with e.g. antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects. The infusion rate may be slowed in order to decrease infusion reactions especially if infusion reactions have occurred previously.

Antibodies to infliximab may develop in some patients. These antibodies have been associated with an increased frequency of infusion reactions and may be associated with an increased risk of serious 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 are not receiving immunosuppressants during infliximab treatment are potentially at greater risk of developing these antibodies. These antibodies cannot always be detected in serum samples. If serious reactions occur, symptomatic treatment must be given and further infliximab infusions must not be administered.

Long-term efficacy of retreatments with infliximab has not yet been established. Reactions following readministration, including delayed hypersensitivity reactions have been observed in a significant number of patients (25% in one clinical trial) with Crohn's disease who were retreated with a liquid formulation of infliximab, which is no longer in use, following a 2 to 4 year period without infliximab treatment. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash within 12 days following retreatment. Some patients also experienced pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and/or headache. These effects have sometimes been described as serum-sickness-like reactions. In post-marketing studies, some patients required steroid therapy to treat the delayed hypersensitivity reaction rather than symptomatic treatment alone. Advise patients to seek immediate medical advice if they experience any delayed adverse event (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Delayed Hypersensitivity). If patients are retreated after a prolonged period, they should be closely monitored for signs and symptoms of delayed hypersensitivity.

Infusion reactions following re-administration of infliximab

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) 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 infliximab maintenance therapy for psoriasis is interrupted, infliximab should be reinitiated as a single dose followed by maintenance therapy.

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

Auto-immune processes

Treatment with infliximab may result in the formation of autoantibodies and in the development of a lupus-like syndrome.

The relative deficiency of TNFα caused by anti-TNF therapy may result in the initiation of an autoimmune process in a subgroup of genetically susceptible patients. If drug-induced lupus is suspected, patients being treated with infliximab should have regular measurements of Antinuclear antibodies (ANA) and double-stranded DNA (dsDNA) antibodies.

If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with infliximab and is positive for antibodies against double-stranded DNA, treatment should be discontinued (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Studies have not been performed to assess the effects of infliximab on the healing of the internal

fistula canal, on closure of non-cutaneously draining fistulas (e.g. entero-entero) or on cutaneously draining fistulas in locations other than perianal and periabdominal.

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-Barre syndrome (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Table 1 & Table 2). Prescribers should exercise caution in considering the use of infliximab in patients with these neurological disorders and should consider discontinuation of infliximab if these disorders develop.

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 (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Table 2). 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 ALT elevations ≥5 times the upper limit of normal develops, infliximab should be discontinued, and a thorough investigation of the abnormality should be undertaken.

As also observed with the use of other immunosuppressive drugs, reactivation of hepatitis B has occurred in patients receiving infliximab who are chronic carriers of this virus (i.e. surface antigen positive). Patients should be tested for Hepatitis B Virus (HBV) infection before initiating treatment with immunosuppressants, including infliximab. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of, during treatment with, and for several months following the discontinuation of infliximab.

Malignancies and lymphoproliferative disorders

In the controlled portions of clinical trials of TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During clinical trials of infliximab in patients with rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, psoriasis, and ulcerative colitis, the incidence of lymphoma in IXIFI-treated patients was higher than expected in the general population, but the occurrence of lymphoma was rare. Furthermore, there is an increased background lymphoma risk even in the absence of TNF blocking therapy in rheumatoid arthritis and Crohn's disease patients with longstanding, highly active, inflammatory disease, and/or active chronic exposure to immunosuppressant therapies, which complicates the risk estimation.

In a clinical trial exploring the use of infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Prescribers should exercise caution when considering the use of infliximab in patients with moderate to severe COPD.

With the current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-blocking agent cannot be excluded (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Paediatric 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-blocking agents (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 (Hodgkin's and non-Hodgkin's lymphoma). 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 lymphomas

Post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF-blocking agents including infliximab (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Table 2). 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.

It is uncertain whether the occurrence of the HSTCL is related to infliximab or infliximab in combination with these other immunosuppressants. When treating patients with inflammatory bowel disease, particularly in adolescents and young adults, consideration of whether to use infliximab alone or in combination with other immunosuppressants should take into account a possibility that there is a higher risk of HSTCL with combination therapy versus an observed increased risk of immunogenicity and hypersensitivity reactions with infliximab monotherapy from the clinical trial data.

Leukaemia

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

Colon Carcinoma/Dysplasia

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 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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.

Skin cancers

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including infliximab (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

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

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 infliximab, including those over 60 years of age.

Concurrent administration of TNF-alpha inhibitor and anakinra

Concurrent administration of etanercept (another agent that inhibits TNFα) and anakinra (a recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist) has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. The safety and efficacy of anakinra used in combination with infliximab has not been established. Therefore, combination of infliximab and anakinra is contraindicated.

Concurrent administration of TNF-alpha inhibitor and abatacept

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

Concurrent Administration with other Biological Therapeutics

There is insufficient information regarding the concomitant use of infliximab with other biological therapeutics used to treat the same conditions as IXIFI. The concomitant use of infliximab with these biologics is not recommended because of the possibility of an increased risk of infection.

Switching between Biological Therapeutics

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

Haematological Events

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving TNF-blockers, including infliximab. 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 infliximab who have ongoing or a history of significant haematological 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 infliximab. Discontinuation of infliximab therapy should be considered in patients who develop significant haematological abnormalities.

Vaccinations

It is recommended that all patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating infliximab therapy.

Live Vaccines/Therapeutic Infectious Agents

In patients receiving anti-TNF therapy, limited data are available on the response to vaccination 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 infliximab is not recommended.

Infant 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 twelve 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. FERTILITY, PREGNANCY AND LACTATION).

Infant exposure via breastmilk

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. FERTILITY, PREGNANCY AND LACTATION).

Therapeutic infectious agents

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 infliximab.

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 titres to a polyvalent pneumococcal vaccine, indicating that infliximab did not interfere with T-cell independent humoral immune responses.

Use in psoriasis

The safety and efficacy of infliximab in combination with other immunosuppressive agents used in psoriasis or with phototherapy have not been studied. Infliximab should not be used in combination with such agents because of the possibility of excessive immunosuppression.

Use in Elderly

No major differences were observed in the pharmacokinetics of infliximab in elderly (65-80 years) rheumatoid arthritis patients. The incidence of serious infections in infliximab-treated patients 65 years and older was greater than in those under 65 years of age. In addition, there is a greater incidence of infections in the elderly population in general, therefore, caution should be used in treating the elderly. Clinical studies of infliximab did not include sufficient numbers of Crohn's disease patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. Studies have not been performed in patients with liver or renal disease.

Since elderly patients have a greater frequency of decreased hepatic, renal and/or cardiac function and a greater frequency of concomitant disease and/or other drug therapy, caution in the treatment of elderly patients is recommended.

Paediatric Use

Children and adolescents (6-17 years)

Treatment with infliximab has not been studied in children and adolescent patients ≤17 years with ankylosing spondylitis, psoriatic arthritis or plaque psoriasis. Treatment with infliximab has not been studied in paediatric patients with ulcerative colitis or Crohn's disease under the age of 6 years. Until safety and efficacy data in the above mentioned groups of paediatric patents are available, such treatment is to be avoided. It should be noted that all children and adolescent patients in the Phase 3 trial in Crohn's disease (REACH) were required to be on a stable dose of either 6-mercaptopurine, azathioprine or methotrexate.

Infliximab was studied in 120 patients (age range 4-17 years old) with active Juvenile Rheumatoid Arthritis (JRA) despite methotrexate. This study did not provide conclusive evidence for the efficacy of infliximab in JRA.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

While specific studies on drug interactions with infliximab have not been conducted, the majority of patients in clinical trials received concomitant medications normally used in Crohn's disease. These medications included antibiotics, (including antiviral agents), corticosteroids, 6-mercaptopurine/azathioprine and aminosalicylates. No interactions were reported.

Because corticosteroids alter electrolyte balance and fluid retention, the volume of distribution of infliximab was greater in patients taking corticosteroids. However, no significant clinical sequelae were apparent.

In rheumatoid arthritis, psoriatic 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 (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Immunogenicity).

In psoriasis, concomitant use of infliximab with other immunosuppressive agents has not been studied (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

No other information is available regarding possible effects of other immunosuppressive drugs or their effects on the pharmacokinetics of infliximab.

Concurrent use of infliximab with other Biological Therapeutics

The combination of infliximab with other biological therapeutics used to treat the same conditions as infliximab, including anakinra and abatacept, is not recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Live Vaccines/Therapeutic Infectious Agents

It is recommended that live vaccines not be given concurrently with infliximab. 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 infant (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 FERTILITY, PREGNANCY AND LACTATION).

It is recommended that therapeutic infectious agents not be given concurrently with infliximab (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.6 Fertility, pregnancy and lactation

Effects on fertility

The effect of infliximab on fertility has not been investigated. No impairment of fertility was observed in a fertility and general reproduction study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα.

Use in pregnancy – pregnancy category C

Infliximab is not recommended for use during pregnancy. It is not known whether infliximab can affect reproductive capacity or can cause foetal harm when administered to a pregnant woman. Women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last infliximab treatment.

Since infliximab does not cross react with TNFα in species other than humans and

chimpanzees, animal reproduction studies have not been conducted. In a developmental toxicity study conducted in mice using an analogous monoclonal antibody that selectively inhibits the functional activity of mouse TNFα, no evidence of maternal toxicity, embryotoxicity or teratogenicity was observed.

As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been detected in the serum of infants up to twelve 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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Use in lactation

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 indicate infliximab has been detected at low levels in human milk at concentrations up to 5% of the maternal serum level.

Limited data from published literature also indicate that infants exposed to infliximab through breast milk had no increase in rates of infections and developed normally.

The consideration of infliximab use during breast-feeding should take into account the treatment benefit of the drug to the mother and health benefits of breast-feeding for the infant. Infliximab should only be used if the treatment benefit to the mother outweighs the potential risks to the breast-fed infant.

4.7 Effects on ability to drive and use machines

Infliximab is unlikely to produce an effect on the ability to drive or operate machinery; however, patients who are fatigued should be cautioned to avoid driving or operating machinery.

4.8 Adverse effects (undesirable effects)

In clinical trials with infliximab, adverse drug reactions (ADRs) reasonably attributable to treatment were observed in 36% of placebo-treated patients and 57% of infliximab-treated patients.

Reasonably-related ADRs are listed in Table 1 by system organ class and frequency. Frequency is based on the excess incidence of the ADR compared with placebo in pooled data from clinical trials involving 227 patients receiving placebo and 1421 patients receiving infliximab (Crohn's disease and rheumatoid arthritis). Most ADRs were mild to moderate in severity. Infusion-related reactions were the most common adverse reactions reported in clinical studies. The most common reason for discontinuation of treatment was infusion-related reactions (dyspnoea, urticaria, hypotension, flushing and headache).

Table 1: Undesirable Effects in Clinical Trials (common >1/100, <1/10; uncommon >1/1000, <1/100; rare <1/1000)

Resistance mechanism disorders	
Common:	Viral infection (e.g. influenza, herpes infections), fever
Uncommon:	Abscess, cellulitis, moniliasis, sepsis, impaired healing, bacterial infection, tuberculosis, fungal infection
Rare	Granulomatous lesion
Neoplasms benign, malignant and unspecified	
Rare:	Lymphoma
Immune disorders	
Common:	Serum-sickness-like reactions
Uncommon:	Autoantibodies, lupus-like syndrome, complement factor abnormality
Rare:	Sarcoid-like reaction
Blood disorders	
Uncommon:	Anaemia, leukopenia, lymphadenopathy, lymphocytosis, lymphopenia, neutropenia, thrombocytopenia
Psychiatric disorders	
Uncommon:	Depression, confusion, agitation, amnesia, nervousness, somnolence, insomnia
Central and peripheral nervous system disorders	
Common:	Headache, vertigo/dizziness
Uncommon:	Exacerbation of demyelinating disease suggestive of multiple sclerosis
Rare:	Meningitis
Vision and hearing disorders	
Uncommon:	Conjunctivitis, endophthalmitis, keratoconjunctivitis
Cardiovascular disorders	
Common:	Flushing
Uncommon:	Ecchymosis/haematoma, hypertension, hypotension, syncope, petechia, thrombophlebitis, palpitation, vasospasm, cyanosis, peripheral ischaemia, arrhythmia, worsening heart failure* bradycardia
Rare:	Circulatory failure, tachycardia
Respiratory system disorders	
Common:	Upper respiratory tract infection, lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, sinusitis
Uncommon:	Epistaxis, bronchospasm, pleurisy, respiratory tract allergic reaction, pulmonary oedema
Rare:	Pleural effusion
Gastrointestinal system disorders	

Common:	Nausea, diarrhoea, abdominal pain, dyspepsia
Uncommon:	Constipation, gastro-oesophageal reflux, cheilitis, diverticulitis, intestinal obstruction
Rare:	Intestinal perforation, intestinal stenosis, gastrointestinal haemorrhage
Liver and biliary system disorders	
Common:	Abnormal hepatic function
Uncommon:	Cholecystitis
Rare:	Hepatitis
Skin and appendages disorders	
Common:	Rash, pruritus, urticaria, increased sweating, dry skin
Uncommon:	Fungal dermatitis/onychomycosis, eczema/seborrhoea, hordeolum, bullous eruption, furunculosis, periorbital oedema, hyperkeratosis, rosacea, verruca, abnormal skin pigmentation/colouring, alopecia
Musculoskeletal system disorders	
Uncommon:	Myalgia, arthralgia, back pain
Urinary system disorders	
Uncommon:	Urinary tract infection, pyelonephritis
Reproductive disorders	
Uncommon:	Vaginitis
Body as a whole general disorders	
Common:	Fatigue, chest pain, infusion-related reactions
Uncommon:	Oedema, hot flushes, infusion syndrome, pain, chills/rigors, anaphylactic reactions
Administration/application site disorders	
Uncommon:	Injection site reactions
Investigations	
Uncommon:	Weight increased**

*reported in early phase studies evaluating infliximab in patients with congestive heart failure

** At month 12 of the controlled period for adult clinical trials across all indications, the median weight increase was 3.50 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects. The median weight increase for inflammatory bowel disease indications was 4.14 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects, and the median weight increase for rheumatology indications was 3.40 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects.

Vomiting and elevated hepatic transaminases were also reported.

Children and adolescent patients

Paediatric Crohn's disease (children and adolescents (6-17 years))

In general, the adverse events in children and adolescent patients who received infliximab were similar in frequency and type to those seen in adult Crohn's disease patients. Differences from adults and other special considerations are discussed in the following paragraphs.

The following adverse events were reported more commonly in 103 children and adolescent Crohn's disease patients randomised at week 10 administered 5 mg/kg infliximab through 54 weeks (out of a total of 112 patients who entered the REACH trial, see also Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials) than in adult Crohn's disease patients receiving a similar treatment regimen (ACCENT 1 trial, see also Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials): anaemia (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%).

Infusion-related reactions

Overall, in REACH, 17.5% of randomised patients experienced 1 or more infusion reactions, with 17.0% and 18.0% of patients in the 8-weekly and 12-weekly maintenance treatment groups, respectively. There were no serious infusion reactions, and 2 subjects in REACH had non-serious anaphylactic reactions.

Immunogenicity

Antibodies to infliximab developed in 3 (2.9%) children and adolescent patients.

Infections

Infections were reported in 56.3% of randomised children and adolescent subjects treated with infliximab (REACH trial), and in 50.4% of subjects in adult's Crohn's (ACCENT 1 trial). In the REACH trial, infections were reported more frequently for subjects who received 8-weekly as opposed to 12-weekly infusions (73.6% and 38.0%, respectively), while serious infections were reported for 3 subjects in the q8 week and 4 subjects in the 12-weekly maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported in 3 patients, 2 in the 8-weekly and 1 in the 12-weekly maintenance treatment groups. Herpes zoster was reported in 2 patients in the 8-weekly maintenance treatment group.

Paediatric ulcerative colitis (children and adolescents (6-17 years))

Overall proportions of patients with adverse events and serious adverse events were generally consistent in the paediatric ulcerative colitis and adult ulcerative colitis (ACT 1 and ACT 2) studies. In the paediatric ulcerative colitis study (C0168T72), the most common adverse event was worsening of ulcerative colitis, the incidence of which was higher in patients on every 12 week vs. the every 8 week dosing regimen. In 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 ulcerative colitis.

Infections

Infections were reported in 31 (51.7%) of 60 treated patients in C0168T72 and 22 (36.7%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in C0168T72 was similar to that in the paediatric 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 C0168T72, 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 C0168T72, 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 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%]).

Infusion-related reactions

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.

Immunogenicity

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

Post-marketing Experience:

During post-marketing experience, a rare type of hepatosplenic T-cell lymphoma has been reported in patients treated with infliximab with the vast majority of cases occurring in Crohn's disease or ulcerative colitis and most of whom were adolescent or young adult males (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Juvenile Rheumatoid Arthritis (JRA)

Infliximab was studied in a trial in 120 patients (age range: 4-17 years old) with active JRA despite methotrexate. Patients received 3 mg/kg infliximab or placebo intravenously at weeks 0, 2, and 6. Subjects randomised to placebo crossed over to receive 6 mg/kg infliximab at weeks 14, 16 and 20 and then every 8 weeks through to week 44. Subjects randomised to 3 mg/kg infliximab continued to receive the same dose of infliximab at weeks 14, 20 and then every 8 weeks through to week 44. This study did not provide conclusive evidence for the efficacy of infliximab in JRA.

Infusion reactions

Infusion reactions occurred in 35 % of patients with JRA receiving 3 mg/kg compared with 17.5% of patients receiving 6 mg/kg. In the 3 mg/kg infliximab group, 4 out of 60 patients had a serious infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among the serious infusion reactions). In the 6 mg/kg group, 2 out of 57 patients had a serious infusion reaction, one of whom had a possible anaphylactic reaction.

Immunogenicity

Antibodies to infliximab developed in 38 % of patients receiving 3 mg/kg compared with 12% of patients receiving 6 mg/kg. The antibody titres were notably higher for the 3 mg/kg compared to the 6 mg/kg group.

Infections

Infections occurred in 68% (41/60) of children receiving 3 mg/kg over 52 weeks, 65% (37/57) of children receiving infliximab 6 mg/kg over 38 weeks and 47% (28/60) of children receiving placebo over 14 weeks.

Post-marketing experience

Table 2: Undesirable effects in post marketing reports (common >1/100, <1/10; uncommon >1/1000, <1/100; rare <1/1000; very rare <1/10,000)

Nervous System Disorders	
Rare	Central nervous system demyelinating disorders (such as multiple sclerosis and optic neuritis), cerebrovascular accidents*, peripheral demyelinating disorders (such as Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), neuropathies, numbness, tingling, seizure
Very rare	Transverse myelitis, orbital apex syndrome.
Blood and Lymphatic Disorders	
Rare	Pancytopenia, agranulocytosis (including infants exposed *in utero* to infliximab).
Very rare	Haemolytic anaemia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura
Hepatobiliary System Disorders	
Rare	Hepatitis, hepatitis B reactivation, jaundice, autoimmune hepatitis, liver failure
Very rare	Hepatocellular damage, Hepatosplenic T-cell lymphoma (primarily in adolescents and the vast majority in young adults with Crohn's disease and ulcerative colitis)
Cardiac Disorders	
Uncommon	Arrhythmia*
Rare	Myocardial ischemia/myocardial infarction*
Very rare	Pericardial effusion
Eye disorders	
Very rare	Uveitis
Unknown	Transient visual loss
General Disorders and Administration Site Disorders	
Common	Infusion-related reactions
Uncommon	Anaphylactic reactions
Rare	Anaphylactic shock, cutaneous and systemic vasculitis
Infections and Infestations	
Rare	Opportunistic infections such as atypical mycobacteria, tuberculosis, pneumocystis carinii pneumonia (PCP), histoplasmosis, coccidioidomycosis, cryptococcosis, aspergillosis, listeriosis, candidiasis, and vaccine breakthrough infection (after *in utero* exposure to infliximab)**
Very rare	Salmonellosis
Frequency unknown	Cytomegalovirus (CMV) colitis
Respiratory, Thoracic and Mediastinal Disorders	
Rare	Interstitial pneumonitis/fibrosis
Neoplasm Benign and Malignant	
Rare	Melanoma, leukaemia, mycosis fungoides
Very rare	Merkel cell carcinoma
Frequency unknown	Basal cell carcinoma, squamous cell carcinoma, cervical cancer, paediatric malignancy, Kaposi's sarcoma

Skin and Subcutaneous Tissue Disorders	
Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, linear IgA bullous dermatosis (LABD), acute generalised exanthematous pustulosis (AGEP), lichenoid reactions.

* Within 24 hrs
** including bovine tuberculosis [disseminated BCG infection (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Live Vaccines/Therapeutic Infectious Agents)].

In post-marketing spontaneous reporting, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, paediatric malignancy, leukaemia and vasculitis have been reported. During or within 2 hours of infliximab infusion, transient visual loss, myocardial ischaemia/infarction, and arrhythmia have occurred. Fatal and non-fatal cases of cerebrovascular accidents and myocardial ischaemia/infarction have been reported within 24 hours of infusion. There have also been reports of arrhythmia occurring within 24 hours of infusion. In addition, interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis) has been observed, which in some cases may be rapidly aggressive.

Spontaneous serious adverse events in the postmarking experience with infliximab in the paediatric population have included malignancies, transient hepatic enzyme abnormalities, lupus-like syndromes, and positive autoantibodies.

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

Psoriasis: New-Onset and Exacerbations

Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, have been reported with the use of TNF-blockers, including infliximab. Cases of exacerbation of pre-existing psoriasis have also been reported with the use of TNF-blockers. Many of these patients were taking concomitant immunosuppressants (e.g., MTX, corticosteroids). Some of these patients required hospitalisation. Most patients had improvement of their psoriasis following discontinuation of their TNF-blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF-blocker. Discontinuation of infliximab should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Infusion-related reactions

An infusion related reaction was defined in clinical studies, as any adverse event occurring during an infusion or within 1 hour after an infusion. In phase 3 clinical studies, 18% of infliximab-treated patients compared with 5% of placebo-treated patients experienced an infusion-related reaction. Among all infliximab infusions, approximately 3% of infusions were accompanied by nonspecific symptoms such as fever or chills, <1% were accompanied by pruritus or urticaria, 1% were accompanied by cardiopulmonary reactions (primary chest pain, hypotension, hypertension or dyspnoea) and 0.1% were accompanied by combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Discontinuation of treatment resulted in 2% of patients and all patients recovered with or without medical therapy. Infusion-related effects in patients were more likely to occur during the first (8%) and less likely, on subsequent infusions (second, 7%; third, 6%; and fourth, 5%; etc.).

Patients who became positive for antibodies to infliximab were more likely (approximately 2-

3 fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of infusion-related reactions.

Of infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period.

In the ASPIRE study, 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% of the patients and serious infusion reactions occurred in 0.4% of the patients.

In a post hoc analysis of ten 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). 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.

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.

In a clinical trial of patients with moderate to severe psoriasis designed to assess the efficacy and safety of long-term maintenance therapy versus re-treatment with an induction cycle of infliximab, 4% (8/219) of patients in the intermittent therapy arm experienced serious infusion reactions versus <1% (1/222) in the maintenance therapy arm. Patients enrolled in this trial did not receive any concomitant immunosuppressant therapy. Intermittent therapy in this trial was defined as the re-administration of an induction cycle (maximum of four infusions at 0, 2, 6, and 14 weeks) of infliximab upon disease flare after a period of no treatment. In this study, the majority of serious infusion reactions occurred during the second infusion at Week 2. Symptoms included, but were not limited to, dyspnoea, urticaria, facial oedema, 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 clinical study of 41 patients retreated with a liquid formulation of infliximab, which is no longer in use, following a 2 to 4 year period without infliximab treatment, 10 patients experienced undesirable effects manifesting 3 to 12 days following infusion. In 6 of these patients, the effects were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash. Some patients also experienced pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and/or headache. The clinical data are not adequate to determine if occurrence of these reactions is due to the different formulations administered to these patients in this study. 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 retreatment intervals up to 1 year. In the Phase III psoriasis study, 1% (4/366) of patients experienced symptoms of arthralgia, myalgia, fever and rash early in the treatment course following infliximab infusions.

Immunogenicity

Patients who developed antibodies to infliximab were more likely to develop 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 approximately 24% of patients with any immunosuppressant therapy, and in approximately 37% of patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, approximately 8% of patients developed antibodies to infliximab. In psoriatic arthritis patients who received 5 mg/kg with and without methotrexate, antibodies occurred overall in 15% of patients (antibodies occurred in 4% of patients receiving methotrexate and in 26% of patients not receiving methotrexate at baseline). Of Crohn's disease patients who received maintenance treatment, approximately 6-13% developed antibodies to infliximab. The antibody incidence was 2-3 fold higher for patients treated episodically. Due to methodological shortcomings, 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. In a Phase III psoriasis study in which patients were treated with infliximab induction followed by every 8-week maintenance infusions without concomitant immunosuppressive therapy, antibodies were detected in approximately 20% of patients.

Infections

In clinical studies, 35% of infliximab-treated patients experienced infections compared with 22% of placebo-treated patients. Serious infections, such as pneumonia, were reported in 5% of both infliximab-treated patients and placebo-treated patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In a Phase III psoriasis study, after 24 weeks of follow-up, 1% (3/298) of infliximab-treated psoriasis patients compared to 0% (0/76) of placebo-treated patients developed serious infections.

In post-marketing surveillance, opportunistic infections such as tuberculosis, pneumocystis carinii pneumonia (PCP), histoplasmosis, listeriosis, coccidioidomycosis, aspergillosis and oesophageal candidiasis have been reported.

In post-marketing spontaneous reporting, infections are the most common serious adverse event. Some of the cases have resulted in fatal outcome. Cases of tuberculosis, sometimes fatal, including miliary tuberculosis and tuberculosis with extrapulmonary location (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), and protozoal infections have been reported.

Malignancies and lymphoproliferative disorders

In clinical studies with infliximab, in which 5780 patients were treated, representing 5494 patient-years, 5 cases of lymphomas and 26 non-lymphoma malignancies were detected as compared with no lymphomas and 1 non-lymphoma malignancy in 1600 placebo-treated patients observed during 941 patient years.

In long-term safety follow-up of clinical studies with infliximab of up to 5 years, representing 6234 patient years, 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Malignancies and lymphoproliferative disorders).

In the controlled portions of some clinical trials of the TNF-blocking agents, more cases of non-lymphoma malignancy have been observed among patients receiving a TNF-blocker compared with control patients. 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, 5.7% [95% CI 2.65% - 10.6%] vs. 1% [95% CI 0.03% - 7.0%]. The malignancies were mainly lung and head and neck. All patients had a history of heavy smoking.

A population-based retrospective cohort study 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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

During post-marketing experience, a rare type of hepatosplenic T-cell lymphoma has been reported in adolescent and young adult patients with Crohn's disease treated with infliximab (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Malignancies and lymphoproliferative disorders). There have also been cases of cutaneous T cell lymphoma, mycosis fungoides, reported in the post-marketing setting.

Heart failure

In a phase II study aimed at evaluating infliximab in moderate to severe congestive heart failure (CHF), higher incidence of mortality due to worsening of heart failure was seen in patients treated with infliximab, especially those treated with the higher dose of 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. There have also been post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.

Autoantibodies / Lupus-like Syndrome

In clinical studies approximately 52% of (1261) infliximab-treated patients who were ANA negative at baseline developed a positive ANA during the trial (compared with approximately 19% of 129 placebo-treated patients). Anti-dsDNA antibodies developed in approximately 17% (261) of patients treated with infliximab (compared with 0% of 162 placebo-treated patients. At the last evaluation, 150 of these 261 infliximab-treated patients (57%) remained anti-dsDNA positive. Clinical signs consistent with a lupus-like syndrome remain uncommon.

Hepatobiliary Events

In post-marketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving infliximab (see Table 3). A causal relationship between infliximab and these events has not been established.

In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving infliximab without progression to severe hepatic injury. Elevations of ALT ≥5 x 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.

Table 3: Proportion of patients with increased ALT activity in Clinical Trials

Indication	**Number of patients evaluated for ALT**		**Median follow-up (wks)[3]**		**≥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]	173	703	54.1	54.1	3.5%	5.1%	0.0%	1.7%
Paediatric 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%
Paediatric 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 Phase III 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 randomised to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in the ALT analysis.
[3] Median follow-up is based on patients treated

Comparability of IXIFI with Remicade®

The safety profile was assessed in a Phase I Study B5371001 and a Phase III Study B5371002.

The safety profile of IXIFI was consistent with what has previously been reported for infliximab.

During clinical studies with IXIFI, 49 healthy subjects were exposed to a single dose of IXIFI, 48 to EU Remicade® and 49 to US Remicade®. and 649 patients with rheumatoid arthritis (RA) were exposed to infliximab, (323 patients to IXIFI and 326 patients to EU Remicade®).

During the randomised, double-blind period of Study B5371002, 185 (57.3%) patients from

the IXIFI treatment group and 176 (54.0%) patients from the Remicade® treatment group experienced all causality treatment-emergent adverse events (TEAEs). Sixteen (5.0%) patients from the IXIFI treatment group and 20 (6.1%) patients from Remicade® treatment group reported serious adverse events. The majority of TEAEs were mild to moderate in severity and the frequency of events and severity grades was similar between the treatment groups. Treatment-related TEAEs occurred with similar incidences in both treatment groups A total of 81 (25.1%) patients from the IXIFI treatment group and 75 (23.0%) patients from the Remicade® treatment group experienced TEAEs that were determined to be related to the treatment.

Any TEAEs that occurred in at least 1% of all patients who received IXIFI or Remicade® in the double-blind 30 week randomised period of Study B5371002 are outlined in Table 4.

Table 4. Percent of Participants Reporting Treatment-Emergent Adverse Events >= 1% (All Causality) in B5371002 Study, Treatment Period 1 - Safety Population

		IXIFI (N = 323) 3 mg/kg([a]. Dose level could be increased from Week 14 if necessary)		**REMICADE (N = 326) 3 mg/kg([a]. Dose level could be increased from Week 14 if necessary)**	
		Total		**Total**	
System Organ Class	**Preferred Term**	**n**	**(%)**	**n**	**(%)**
Blood and lymphatic system disorders					
	Anaemia	7	(2.2)	10	(3.1)
	Leukopenia	1	(0.3)	4	(1.2)
	Neutropenia	5	(1.5)	4	(1.2)
Gastrointestinal disorders					
	Abdominal pain upper	5	(1.5)	5	(1.5)
	Diarrhoea	7	(2.2)	8	(2.5)
	Dyspepsia	3	(0.9)	4	(1.2)
	Nausea	7	(2.2)	10	(3.1)
	Vomiting	4	(1.2)	4	(1.2)
General disorders and administration site conditions					
	Pyrexia	3	(0.9)	10	(3.1)
Infections and infestations					
	Bronchitis	14	(4.3)	6	(1.8)
	Gastroenteritis	4	(1.2)	3	(0.9)
	Influenza	5	(1.5)	3	(0.9)

		IXIFI (N = 323) 3 mg/kg([a]. Dose level could be increased from Week 14 if necessary)		**REMICADE (N = 326) 3 mg/kg([a]. Dose level could be increased from Week 14 if necessary)**	
		Total		**Total**	
System Organ Class	**Preferred Term**	**n**	**(%)**	**n**	**(%)**
	Nasopharyngitis	14	(4.3)	13	(4.0)
	Oral herpes	4	(1.2)	3	(0.9)
	Pharyngitis	4	(1.2)	0	(0.0)
	Sinusitis	4	(1.2)	0	(0.0)
	Upper respiratory tract infection	12	(3.7)	13	(4.0)
	Urinary tract infection	6	(1.9)	9	(2.8)
	Viral infection	4	(1.2)	2	(0.6)
Injury, poisoning and procedural complications					
	Contusion	2	(0.6)	6	(1.8)
	Fall	6	(1.9)	3	(0.9)
	Infusion related reaction	19	(5.9)	21	(6.4)
Investigations					
	Alanine aminotransferase increased	19	(5.9)	15	(4.6)
	Aspartate aminotransferase increased	14	(4.3)	11	(3.4)
	Mycobacterium tuberculosis complex test positive	1	(0.3)	4	(1.2)
Musculoskeletal and connective tissue disorders					
	Arthralgia	6	(1.9)	5	(1.5)
	Back pain	4	(1.2)	6	(1.8)
	Osteoporosis	4	(1.2)	2	(0.6)
	Rheumatoid arthritis	6	(1.9)	8	(2.5)
Nervous system disorders					
	Dizziness	2	(0.6)	4	(1.2)
	Headache	10	(3.1)	9	(2.8)
Respiratory, thoracic and mediastinal disorders					
	Dyspnoea	1	(0.3)	6	(1.8)

		IXIFI (N = 323) 3 mg/kg([a]. Dose level could be increased from Week 14 if necessary)		**REMICADE (N = 326) 3 mg/kg([a]. Dose level could be increased from Week 14 if necessary)**	
		Total		**Total**	
System Organ Class	**Preferred Term**	**n**	**(%)**	**n**	**(%)**
Skin and subcutaneous tissue disorders					
	Erythema	2	(0.6)	4	(1.2)
	Pruritus	5	(1.5)	6	(1.8)
	Rash	8	(2.5)	10	(3.1)
	Urticaria	4	(1.2)	2	(0.6)
Vascular disorders					
	Hypertension	14	(4.3)	11	(3.4)
a. Dose level could be increased from Week 14 if necessary					

During the randomised, double-blind period of Study B5371002, the proportions of patients who experienced infections and infestations were (86 [26.6%] patients in the IXIFI treatment group vs. 72 [22.1%] patients in the Remicade® treatment group. A total of 6 (1.9%) patients from the IXIFI treatment group and 9 (2.8%) patients from the Remicade® treatment group were reported to have serious infections and infestations.

The incidence of infusion-related reactions was comparable between the IXIFI and the Remicade® treatment group. A total of 19 (5.9%) patients in the IXIFI treatment group and 21 (6.4%) patients in the Remicade® treatment group were reported to have infusion-related reaction.

Alanine aminotransferase (ALT) elevations were reported in 19 (5.9%) patients in the IXIFI treatment group and 15 (4.6%) patients in the Remicade® treatment group. Aspartate aminotransferase (AST) elevations were reported in 14 (4.3%) patients in IXIFI treatment group and 11 (3.4%) patients in the Remicade® treatment group.

Up to Week 30, anti-drug antibodies developed in 157 (48.6%) patients in the IXIFI treatment group and 167 (51.2%) patients in the Remicade® treatment group, while a total of 124 (79.0%) patients who developed anti-drug antibodies from the IXIFI treatment group and 143 (85.6%) patients from the Remicade® treatment group tested positive for neutralising antibodies.

Following the randomised double-blind period, a total of 280 patients from the IXIFI treatment group continued to receive IXIFI (IXIFI/IXIFI), 143 patients from Remicade® treatment group continued to receive Remicade® (Remicade®/Remicade®) and 143 patients from the Remicade® treatment group were switched from Remicade® to receive IXIFI (Remicade®/IXIFI) from Week 30 to Week 54 as part of a transition-extension period.

A total of 103 (36.8%) patients from IXIFI/IXIFI treatment group, 54 (37.8%) patients from Remicade®/IXIFI treatment group and 48 (33.6 %) patients from the Remicade®/Remicade® treatment group experienced newly occurring TEAE. 13 (4.6%) patients from the IXIFI/IXIFI treatment group, 4 (2.8%) patients from Remicade®/IXIFI treatment group and 11 (7.7%) patients from the Remicade®/Remicade® treatment group experienced serious TEAEs.

TEAEs that occurred in at least 2% of all patients who received IXIFI or Remicade® in transition-extension treatment period 2 are outlined in Table 5.

Table 5. TEAEs That Occurred in >= 2% (All Causality) of All Participants Who Received IXIFI or REMICADE in B5371002 During Treatment Period 2 - Safety Population

		IXIFI/ IXIFI (N = 280) 3 mg/kg[a]		REMICADE/ IXIFI (N = 143) 3 mg/kg[a]		REMICADE/ REMICADE (N = 143) 3 mg/kg[a]	
		Total		Total		Total	
System Organ Class	**Preferred Term**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Gastrointestinal disorders							
	Nausea	1	(0.4)	1	(0.7)	4	(2.8)
Infections and infestations							
	Bronchitis	3	(1.1)	2	(1.4)	3	(2.1)
	Nasopharyngitis	9	(3.2)	2	(1.4)	5	(3.5)
	Upper respiratory tract infection	6	(2.1)	3	(2.1)	2	(1.4)
	Urinary tract infection	3	(1.1)	3	(2.1)	2	(1.4)
Injury, poisoning and procedural complications							
	Infusion related reaction	9	(3.2)	6	(4.2)	12	(8.4)
Musculoskeletal and connective tissue disorders							
	Arthralgia	0	(0.0)	3	(2.1)	1	(0.7)
	Joint swelling	6	(2.1)	1	(0.7)	1	(0.7)
	Rheumatoid arthritis	5	(1.8)	3	(2.1)	4	(2.8)
Respiratory, thoracic and mediastinal disorders							
	Dyspnoea	0	(0.0)	1	(0.7)	3	(2.1)
Skin and subcutaneous tissue disorders							
	Erythema	0	(0.0)	0	(0.0)	3	(2.1)
	Rash	3	(1.1)	3	(2.1)	0	(0.0)
Vascular disorders							
	Flushing	0	(0.0)	3	(2.1)	0	(0.0)

		IXIFI/ IXIFI (N = 280) 3 mg/kg[a]		REMICADE/ IXIFI (N = 143) 3 mg/kg[a]		REMICADE/ REMICADE (N = 143) 3 mg/kg[a]	
		Total		Total		Total	
System Organ Class	**Preferred Term**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
	Hypertension	4	(1.4)	2	(1.4)	3	(2.1)

a. Dose level could be increased from Week 14 if necessary, one time only.
Includes all AEs collected since the first infusion of study drug in treatment period 2, and AEs that were ongoing at the start of treatment period 2, up to 8 weeks from the last study treatment dosing.

During the transition-extension treatment period 2 of Study B5371002, the proportions of patients who experienced infections and infestations were: 45 (16.1%) patients in the IXIFI/IXIFI treatment group, 19 (13.3%) patients in the Remicade®/IXIFI treatment group, and 21 (14.7%) patients from the Remicade®/Remicade® treatment group.

A total of 9 (3.2%) patients from the IXIFI/IXIFI treatment group, 6 (4.2%) patients from the Remicade®/IXIFI treatment group and 12 (8.4%) patients from the Remicade®/Remicade® were reported to have newly occurring TEAEs associated with infusion-related reactions.

During the transition-extension period, 146 (52.1%) patients from the IXIFI/IXIFI treatment group, 83 (58.0%) patients from the Remicade®/IXIFI treatment group and 86 (60.1%) patients from the Remicade®/ Remicade® treatment group had at least one ADA positive results between Week 30 and Week 54. For NAb, 118 (80.8%) patients in the IXIFI/IXIFI treatment group, 65 (78.3%) patients in the Remicade®/IXIFI treatment group and 73 (84.9%) patients from the Remicade®/ Remicade® treatment had at least one positive NAb results between Week 54 and Week 78.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Infliximab is a chimeric human-murine monoclonal antibody that binds to human tumour necrosis factor alpha (TNFα). TNFα is a pro-inflammatory and immunoregulatory cytokine that, when overexpressed, mediates chronic inflammation in diseases such as Crohn's disease and rheumatoid arthritis. Cellular responses to TNFα include:

- up-regulation of other pro-inflammatory cytokines such as interleukin (IL) 1 and IL-12
- up-regulation of chemokines such as IL-8
- priming and activation of neutrophils
- up-regulation of adhesion molecules and tissue factor by endothelial cells
- induction of proliferation and increased synthesis of IL-6 and metalloproteinases by fibroblasts.

Infliximab neutralises 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 neutralise TNFβ (lymphotoxin α), a related cytokine that utilises the same receptors as TNFα.

Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as IL-1 and IL-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 and induction of acute phase and other liver proteins. Cells expressing transmembrane TNFα bound by infliximab can be lysed in vitro by complement or effector cells. Infliximab inhibits the functional activity of TNFα in a wide variety of in vitro bioassays utilising human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells.

Elevated concentrations of TNFα have been found in the sera and stools of adult Crohn's disease patients and in the joints of rheumatoid arthritis patients and correlate with elevated disease activity. Increased concentrations of TNFα have also been found in joint fluid/tissue and in psoriatic skin lesions in patients with psoriatic arthritis. In psoriatic arthritis, treatment with infliximab resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin as well as a reduction of macrophages in the synovium. In patients with Crohn's disease, treatment with infliximab reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine; it also reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon γ. In patients with rheumatoid arthritis, treatment with infliximab reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion, chemoattraction and tissue degradation. After treatment with infliximab, patients with rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to their baseline values. In patients with rheumatoid arthritis, peripheral blood lymphocytes further showed no significant decrease in number or in

proliferative responses to in vitro mitogenic stimulation when compared to untreated patients' cells. In psoriasis patients, treatment with infliximab resulted in decreases in epidermal inflammation and normalisation of keratinocyte differentiation in psoriatic plaques.

Clinical trials

Adult Rheumatoid Arthritis

The safety and efficacy of infliximab were assessed in two multicentre, randomised, double-blind, pivotal trials: ATTRACT (Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy) and ASPIRE (Active-controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset). Concurrent use of stable doses of folic acid, oral corticosteroids (≤ 10 mg/day) and/or non-steroidal anti-inflammatory drugs was permitted.

The primary endpoints were the reduction of signs and symptoms as assessed by the American College of Rheumatology (ACR) criteria (ACR20 for ATTRACT, landmark ACR-N at week 54 for ASPIRE), the prevention of structural 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: evaluator's global assessment, patient's global assessment, functional/disability measure, visual analogue pain scale and erythrocyte sedimentation rate or CRP. ACR-N uses the same criteria as the ACR20, calculated by taking the lowest percentage 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, through week 54, in physical function.

The ATTRACT trial evaluated responses at 30 weeks (reduction in signs and symptoms), 54 weeks (the prevention of structural damage) and 102 weeks (the improvement in physical function) in a placebo-controlled study of 428 adult 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, total van der Heijde-modified Sharp score and HAQ are shown in Table 6. Higher degrees of clinical response (ACR20, ACR50 and ACR70) were observed with infliximab versus methotrexate alone at 30 and 54 weeks compared with methotrexate alone (Table 4).

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 6).

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 6: Effects on ACR 20% Structural Joint Damage and Physical Function at week 54 (ATTRACT)

	Infliximab[a]					
	Control[a]	**3 mg/kg q 8 wks**	**3 mg/kg q 4 wks**	**10 mg/kg q 8 wks**	**10 mg/kg q 4 wks**	**All Infliximab**
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 to week 54[b] (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]	4.0	0.5	0.1	0.5	-0.5	0.0
(Interquartile range)	(0.5, 9.7)	(-1.5, 3.0)	(-2.5, 3.0)	(-1.5, 2.0)	(-3.0, 1.5)	(-1.8, 2.0)
Pts 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	0.5 ± 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 naive patients with early (≤3 years disease duration) active rheumatoid arthritis. Patients randomised had a median age of 51 years with a median disease duration of 0.6 years, and median swollen and tender joint count of 19 and 31, respectively. All patients received methotrexate (optimised to 20

mg/wk 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.

In this trial, infusions were to be administered over 2 hours for the first 3 infusions. The duration of subsequent infusions could be shortened to not less than 40 minutes in patients who did not experience serious infusion reactions. Sixty-six per cent of the patients received at least one shortened infusion of 90 minutes or less and 44% received at least one shortened infusion of 60 minutes or less.

After 54 weeks of treatment, both doses of infliximab + 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 structural damage was observed at weeks 30 and 54 in the infliximab + methotrexate groups compared to methotrexate alone.

Table 7: Effects on ACRn Structural Joint Damage and Physical Function at week 54 ASPIRE

	Placebo + MTX	**Infliximab + MTX**		
		3 mg/kg	**6 mg/kg**	**Combined**
Subjects randomised	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 3mg/kg and 6mg/kg treatment groups respectively vs. placebo + MTX.

Data to support infliximab dose adjustment in rheumatoid arthritis comes from both ATTRACT and ASPIRE, as well as from the START study. START was a randomised, multicentre, double-blind, 3-arm, parallel-group safety study. In one of the arms the secondary objective was to assess the safety and efficacy of dose escalation above 3 mg/kg of infliximab

in 1.5 mg/kg increments to a maximum of 9 mg/kg, given every 8 weeks in subjects with an inadequate response to 3 mg/kg at week 22 or if a flare occurred later. Results are shown in Table8.

Table 8: Summary of responders by number of dose escalations (START)

	n	**Responders n (%)**
Patients in the study at Week 22	329	220 (66.9%)[a]
Patients who were dose escalated[b]	100	
Patients who received 1 dose escalation (final dose 4.5 mg/kg)	59	51 (86.4%)[c]
Patients who received 2 dose escalations (final dose 6.0 mg/kg)	21	17 (81.0%)[c]
Patients who received 3 dose escalations (final dose 7.5 mg/kg)	13	12 (92.3%)[c]
Patients who received 4 dose escalations (final dose 9.0 mg/kg)	7	0 (0.0%)[c]

a: responders are defined as subjects who achieved an ACR20 response at week 22
b: patients who met the criteria for dose escalation at week 22 or thereafter
c: responders are defined as subjects who achieved at least 20% improvement in the number of tender and swollen joints from baseline at 8 weeks after the last dose escalation

Rheumatoid arthritis associated anaemia

Evidence suggests that TNFα plays a role in the inhibition of erythropoiesis in chronic inflammatory disease. In three clinical trials in patients with rheumatoid arthritis (ATTRACT, ASPIRE, START), 39.8 % of patients with a baseline haemoglobin <12 g/dL had an increase in haemoglobin ≥1 g/dL at week 22 when receiving infliximab plus methotrexate, versus 19.3 % in those receiving methotrexate alone (p<0.001). Additionally, 12.1 % of patients treated with infliximab plus methotrexate had an increase ≥2 g/dL in haemoglobin vs. 4.5% of patients in the methotrexate arm alone (p<0.001). Significant results were also found for patients with baseline haemoglobin <10 g/dL.

Analyses of the data from ASPIRE showed that infliximab therapy improved rheumatoid arthritis associated anaemia in both ACR20 responders and non-responders.

Patients with anaemia at baseline (<12 g/dL), % 1 g/dL Hb increase			
	Placebo + MTX	**Infliximab 3 mg/kg + MTX**	**Infliximab 6 mg/kg + MTX**
ACR 20 responders	21/58 (36.2%)	38/69 (55.1%)	35/70 (50.0%)
ACR 20 non-responders	5/23 (21.7%)	8/24 (33.3%)	10/19 (52.6%)

Furthermore, it showed that among ACR20 responders, infliximab 3 mg/kg plus methotrexate improved anaemia significantly (p=0.034) better than methotrexate alone. Improvement in haemoglobin significantly correlated with improvement in physical function and quality of life at week 22.

Ankylosing Spondylitis

Efficacy and safety of infliximab were assessed in two multicentre, double-blind, placebo-controlled studies in patients with active ankylosing spondylitis (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥ 4 and spinal pain ≥ 4 on a scale of 1-10). Improvement in signs and symptoms was measured using the ASAS 20 response criteria and/or the BASDAI 50. Improvement in physical function was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI). Improvement in range of axial motion was evaluated using both the Bath Ankylosing Spondylitis Metrology Index (BASMI) and/or clinical measurements of chest expansion. Health-related Quality of Life was assessed using the SF-36 (physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health). The BASDAI measures disease activity on the basis of six questions relating to fatigue, spinal pain, peripheral arthritis, enthesitis (inflammation at the points where tendons/ligaments/joint capsule enter the bone), and morning stiffness.

In the first study (P01522), which had a 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. After the first year of the study, 53 patients continued into an open-label extension to week 102.

At week 12, 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 to 9% of placebo patients ($p<0.01$). The absolute difference in the BASDAI score compared with placebo at week 12 was 2.4. At 54 and 102 weeks there were 54 and 49 subjects still on infliximab treatment and among those, 34 (63%) and 30 (61%) were BASDAI 50 responders. Improvement was observed as early as week 2, and was maintained through week 102. Physical function range of motion, and quality of life (SF-36) were improved similarly.

In the second trial (ASSERT), 279 patients (78 patients in the placebo group and 201 in the infliximab group) were randomised to receive either placebo (Group 1) or 5 mg/kg infliximab (Group 2) at 0, 2 and 6 weeks and every 6 weeks thereafter through to week 96. At week 24, patients receiving placebo (Group 1) received 5 mg/kg infliximab every 6 weeks through to week 96. Starting with the week-36 infusion and continuing through the week-96 infusion, a patient in Group 2 who had a BASDAI ≥3 at 2 consecutive visits received a 7.5 mg/kg infliximab infusion and continued to receive 7.5 mg/kg infliximab infusions every 6 weeks thereafter through week 96.

At 24 weeks, the primary efficacy timepoint, improvement in signs and symptoms, as measured by the proportion of patients achieving an ASAS 20 response, was 61% in the infliximab-treated group vs. 19% in the placebo group ($p<0.001$). The improvement was observed as early as week 2. Significant improvement in signs and symptoms was also assessed by the BASDAI, with 51% of infliximab-treated subjects achieving at least 50% reduction from baseline in BASDAI score (mean baseline score was 6.5 in the infliximab group and 6.2 in the placebo group), compared with 10.7% of placebo patients ($p<0.001$). The median improvement from baseline in range of axial motion, as assessed by the BASMI was 1.0 for the infliximab-treated group vs. 0.0 for the placebo group ($p=0.019$). The median percent improvement from baseline in chest expansion was 17% for the infliximab-treated group and 0% for the placebo group

(p=0.037). Physical function and quality of life as measured by the BASFI and the SF-36 were also improved significantly at week 24.

All improvements were maintained through week 102 and patients who crossed over to infliximab from placebo at week 24 showed improvement in all scores that were similar to the infliximab-treated group at week 102.

There is no evidence available to suggest that infliximab therapy is able to retard the progression of joint damage or deformity caused by ankylosing spondylitis.

Psoriatic arthritis

Efficacy and safety were assessed in two multicentre, double-blind, placebo-controlled studies in patients with active psoriatic arthritis.

In the first study (IMPACT), efficacy and safety of infliximab were studied 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) with one or more of the following subtypes: arthritis involving DIP joints, arthritis mutilans, asymmetric peripheral arthritis, polyarticular arthritis, and spondylitis with peripheral arthritis. Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Forty-six percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). Patients had previously been treated with NSAIDs (81.5%), DMARDs (79.5%) and corticosteroids (29.0%). 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, 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, PASI and Physical Function in IMPACT and IMPACT 2

	IMPACT				IMPACT 2		
	Placebo (Week 16)	**Infliximab (Week 16)**	**Infliximab[b] (Week 50)**	**Infliximab (Week 98)**	**Placebo (Week 24)**	**Infliximab (Week 24)**	**Infliximab (Week 54)**
Patients randomised	**52**	**52**	**52**	**N/A[a]**	**100**	**100**	**100**
ACR response (% of patients)							
N	52	52	49	78	100	100	76
ACR20 response*	5 (10%)	34 (65%)	34 (69%)	48 (62%)	16 (16%)	54 (54%)	48 (63%)
ACR50	0 (0%)	24 (46%)	26 (53%)	35 (45%)	4 (4%)	41(41%)	32 (42%)

response*							
ACR70 response*	0 (0%)	15 (29%)	19 (39%)	27 (35%)	2 (2%)	27 (27%)	20 (26%)
PASI response (% of patients)b							
N	16	22	22	25	87	83	61
PASI 50 response*	0 (0%)	22 (100%)	19 (86%)	19 (76%)	7 (8%)	62 (75%)	42 (69%)
PASI 75 response*	0 (0%)	15 (68%)	13 (59%)	16 (64%)	1 (1%)	50 (60%)	31 (51%)
PASI 90 response*	0 (0%)	8 (36%)	9 (41%)	12 (48%)	0 (0%)	32 (39%)	26 (43%)
HAQ (% improvement from baseline)c							
N	51	51	48	77	95	94	76
Mean (+ SD)*	-2% (8)	50% (8)	43% (9)	38% (72)	-19% (103)	46% (42)	43% (96)

[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

[e] HAQ=Health Assessment Questionnaire

[*] p<0.01for infliximab vs. placebo at week 16 in IMPACT; 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. The responses were similar regardless of concomitant use of methotrexate.

Treatment with infliximab also resulted in significant improvements in measures of disease activity, including swollen joints, tender joints, dactylitis, and enthesopathy as compared to placebo in both trials.

In the IMPACT and IMPACT 2 studies, 31% and 12% respectively of patients randomised to infliximab at baseline achieved a major clinical response (defined as achieving an ACR70 response at all visits for a continuous 24-week period) at week 98 and week 54 respectively. In contrast, 0% of patients in the placebo group in IMPACT (p<0.001) and 2% of patients in the placebo group in IMPACT 2 (p=0.006) achieved an ACR70 response at the last visit before receiving infliximab therapy.

Radiographic changes were assessed in the IMPACT2 study. Radiographs of both the hands and feet were collected at baseline, weeks 24 and 54 in all patients. Infliximab treatment inhibited the progression of structural damage compared with placebo treatment at the Week 24 primary endpoint as measured by change from baseline in total modified vdH-S score. Differences between infliximab and placebo groups at week 24 were statistically significant for total modified vdH-S score, hands, feet, erosion and joint space narrowing (JSN) scores. Significantly more subjects in the placebo group had readily apparent radiographic progression at week 24 in total modified vdH-S, erosion, and JSN scores compared with the proportion of subjects in the infliximab group. The maintenance of radiographic benefit was observed through 1 year.

The change from baseline at weeks 24 and 54 in the total modified vdH-S score in IMPACT 2

is presented in the table below:

Table 10: Summary of change from baseline in total modified van der Heijde modified Sharp score at weeks 24 and 54 (IMPACT 2)

	Placebo / infliximab 5 mg/kg*	**Infliximab 5 mg/kg**
Subjects randomised	100	100
Change from baseline		
n	100	100
Week 24 Mean ± SD p-value	0.82 ± 2.62	-0.70 ± 2.53 <0.001
Week 54 Mean ± SD p-value	0.53 ± 2.60	-0.94 ± 3.40 <0.001
*placebo patients crossed over to infliximab at week 24		

Infliximab-treated patients also 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 multicentre, randomised, 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. Marked responders were identified as patients who achieved ≥ 90% improvement in PASI from baseline.

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 3mg/kg or, 5 mg/kg infliximab or placebo infusions at weeks 0, 2 and 6. Patients with a physician's global assessment (PGA) score ≥ 3 were eligible to receive an additional infusion of the same treatment at week 26.

In SPIRIT, the median baseline BSA was 27.0%, the median baseline PASI score was 18.9; 62.2% of patients had a baseline PGA score of "moderate" and 24.9% of patients had a baseline PGA score of "marked" or "severe." Prior therapy with PUVA, methotrexate, ciclosporin or acitretin had been received by 81.5% of the patients. The proportion of patients with ≥ 75% improvement in PASI from baseline (PASI 75) at week 10 was 79.8% in the combined infliximab group, 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 ($p<0.001$ for each infliximab versus placebo comparison). At week 10, a significantly greater proportion of infliximab-treated patients, both in the combined group (51.5%) and in the individual groups (3 mg/kg: 45.5%; 5 mg/kg: 57.6%), achieved a marked response (≥ 90% improvement in PASI from baseline) compared to the placebo-treated patients (2.0%). In the 3 mg/kg group, 60.6% of patients maintained response

through week 14 and 75.3% of patients in the 5 mg/kg group maintained response through week 18. 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, suggesting the need for maintenance therapy.

Health related Quality of Life, was assessed with the Dermatology Life Quality Index (DLQI). The median baseline DLQI was 12. The median change from baseline in DLQI at week 10 was -8.0 and -10.0 for the infliximab 3 mg/kg and 5 mg/kg groups, respectively, compared with 0.0 in the placebo group ($p<0.001$ for all infliximab versus placebo comparisons), demonstrating a substantial improvement in quality of life for patients on infliximab therapy.

EXPRESS evaluated the efficacy of infliximab induction and maintenance therapy in 378 patients with plaque psoriasis who were candidates for phototherapy or systemic therapy. 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).

In EXPRESS, the median baseline BSA was 29%, the median baseline PASI score was 21.1 and the majority of patients (89.9%) had a PGA score of moderate, marked, or severe. Prior therapy with PUVA, methotrexate, ciclosporin, or acitretin had been received by 71.4% of patients. At week 10 PASI 75 response was achieved by 80.4% in the infliximab group vs. a placebo group rate of 2.6%, $p<0.001$). Median time to PASI 75 was between 2 and 6 weeks. Improvement in PASI was consistent across subgroups defined by baseline demographics, clinical disease characteristics and psoriasis medication history. Marked responses (PASI 90) at week 10 were achieved by 57.1% of the infliximab group compared to 1.3% in the placebo group ($p<0.001$). The response was maintained through the 24 weeks, the placebo-controlled period. PASI response rates through week 50 are presented in Table 11.

Table 11: Summary of PASI Response Through Week 50 by Visit, EXPRESS

	Placebo → Infliximab 5 mg/kg (at week 24)	**Infliximab 5 mg/kg**	**P-value**
Week 2			
n	77	298	
≥ 90% improvement	0 (0.0%)	3 (1.0%)	
≥ 75% improvement	0 (0.0%)	16 (5.4%)	
≥ 50% improvement	3 (3.9%)	106 (35.6%)	
Week 6			
n	77	295	
≥ 90% improvement	1 (1.3%)	94 (31.9%)	
≥ 75% improvement	4 (5.2%)	184 (62.4%)	
≥ 50% improvement	6 (7.8%)	264 (89.5%)	
Week 10			
n	77	301	
≥ 90% improvement	1 (1.3%)	172 (57.1%)	<0.001
≥ 75% improvement	2 (2.6%)	242 (80.4%)	<0.001
≥ 50% improvement	6 (7.8%)	274 (91.0%)	

	Placebo → Infliximab 5 mg/kg (at week 24)	**Infliximab 5 mg/kg**	**P-value**
Week 24			
n	77	276	
≥ 90% improvement	1 (1.3%)	161 (58.3%)	<0.001
≥ 75% improvement	3 (3.9%)	227 (82.2%)	<0.001
≥ 50% improvement	5 (6.5%)	248 (89.9%)	
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%)	

At week 10, 82.9% of infliximab patients achieved a PGA score of minimal or cleared compared to 3.9% of placebo patients (p<0.001). PGA scores at weeks 6, 10, 24 and 50 are presented in Table 12.

Table 12: Summary of PGA Scores Through Week 50 by Visit, EXPRESS

	Placebo → Infliximab 5 mg/kg (at week 24)	**Infliximab 5 mg/kg**	**p-value**
Week 2			
n	77	298	
PGA of cleared (0) or minimal (1)	3 (3.9%)	59 (19.8%)	
PGA of cleared (0), minimal (1), or mild (2)	9 (11.7%)	208 (69.8%)	
Week 6			
n	77	295	
PGA of cleared (0) or minimal (1)	2 (2.6%)	205 (69.5%)	
PGA of cleared (0), minimal (1), or mild (2)	16 (20.8%)	272 (92.2%)	
Week 10			
n	77	292	
PGA of cleared (0) or minimal (1)	3 (3.9%)	242 (82.9%)	< 0.001
PGA of cleared (0), minimal (1), or mild (2)	14 (18.2%)	275 (94.2%)	< 0.001
Week 24			
n	77	276	
PGA of cleared (0) or minimal (1)	2 (2.6%)	203 (73.6%)	< 0.001
PGA of cleared (0), minimal (1), or mild (2)	15 (19.5%)	246 (89.1%)	< 0.001
Week 50			
n	68	281	
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%)	

The median baseline value for the DLQI was 12.5. The mean baseline values were 45.6 for the

SF-36 physical component and 45.7 for the mental component. Quality of Life improved significantly compared to placebo at weeks 10 and 24 when evaluated by both DLQI and SF-36.

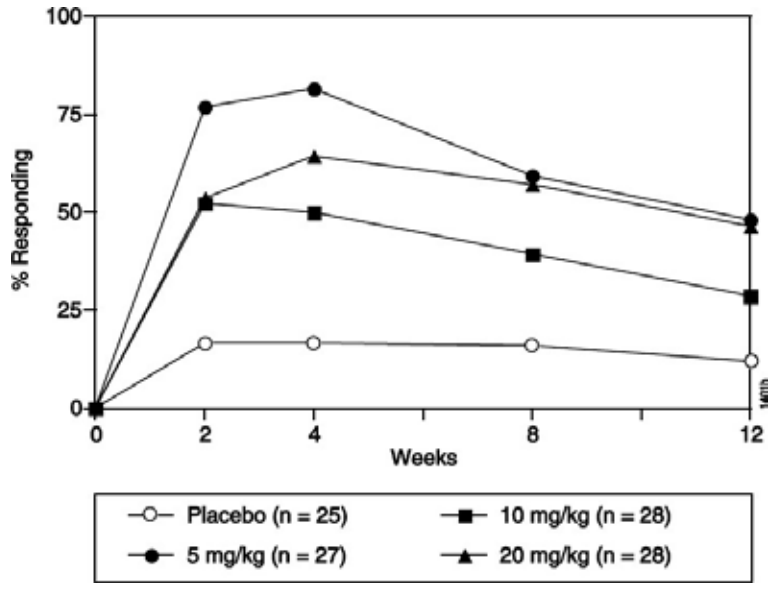
The median baseline NAPSI score for nail psoriasis was 4 and the median number of nails involved with psoriasis was 10. Patients treated with infliximab showed a clear improvement in nail psoriasis from baseline compared to placebo-treated patients, as measured by NAPSI score, and by the decrease in number of nails involved.

Moderate to severe active Crohn's Disease in adult patients (≥18 years)

The safety and efficacy of single and multiple doses of infliximab were assessed in two randomised, double-blind, placebo-controlled studies in patients with moderate to severe active Crohn's disease, with Crohn's Disease Activity Index (CDAI) of 220 to 400 with an inadequate response to prior conventional therapies. Concurrent use of stable dose regimens of corticosteroids, 5-aminosalicylic acid (5-ASA), 6-mercaptopurine (6-MP) and/or azathioprine (AZA) was permitted and 92% of patients continued to receive at least one of these medications.

In the single dose trial of 108 patients, 22 of 27 (81%) of the infliximab-treated patients receiving a 5 mg/kg dose achieved a clinical response (decrease in CDAI by ≥70 points) vs. 4 of 25 (16%) of the placebo-treated patients ($p<0.001$). Also at week 4, 13 of 27 (48%) of infliximabtreated patients achieved a clinical remission (CDAI <150) vs. 1 of 25 (4%) of placebo-treated patients. Results are shown in Figure 1.

Figure 1: Response (≥ 70 point decrease in CDAI) to a Single IV infliximab or Placebo Dose

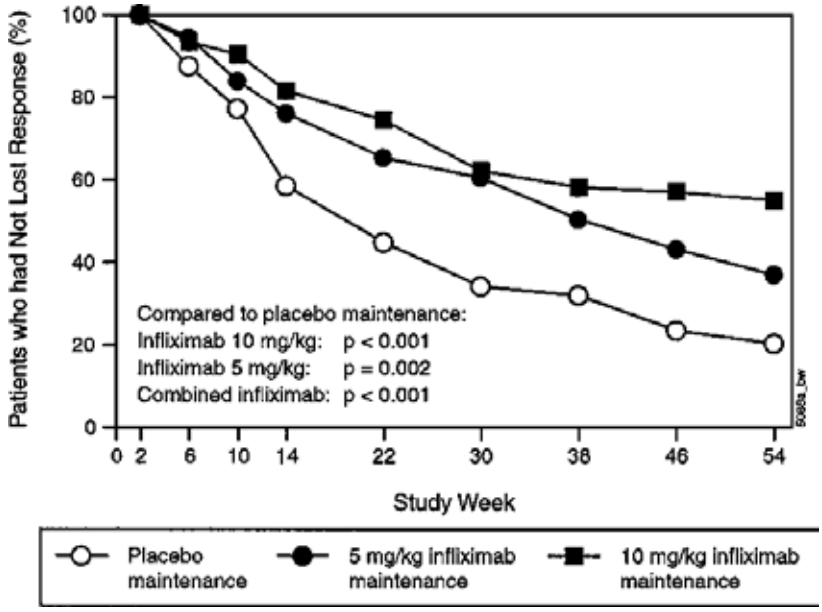


In the multidose trial, 573 patients, with a score of at least CDAI 220, received 5 mg/kg at week 0. After assessment of response, patients were randomly assigned to one of three treatment groups; placebo at weeks 2 and 6 and then every 8 weeks until week 46; 5 mg/kg at weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group, which received 5 mg/kg at weeks 2 and 6, and then 10 mg/kg every 8 weeks. The prespecified co-primary endpoints were the proportion of patients who responded at week 2 and were in remission (CDAI <150)

at week 30 and the time to loss of response in patients who responded. Analyses of the endpoints were on the intent to treat patient population.

At week 2, 58% (335/573) of patients had responded to a single infusion of infliximab and were in clinical response (decrease in CDAI ≥25% and ≥70 points). At week 30, 23 of 110 (21%) of placebo patients were in remission, compared with 44 of 113 (39%) of 5 mg/kg maintenance group (p=0.003) and 50 of 112 (45%) (p=0.0002) of 10 mg/kg maintenance group. Patients in the infliximab maintenance groups had significantly longer time to loss of response than patients in the placebo maintenance group (p<0.001) (Figure 2). Median time to loss of response was 46 weeks in the combined infliximab maintenance treatment group versus 19 weeks in the placebo maintenance group. Patients who achieved a response and subsequently lost response were eligible to receive infliximab on an episodic basis at a dose that was 5 mg/kg higher than the dose to which they were randomised. Eighty-nine percent (50/56) of patients who lost clinical response on infliximab 5 mg/kg every-eight-week maintenance dosing, responded to a 10 mg/kg infliximab infusion.

Figure 2: Kaplan-Meier Estimate of the Proportion of Patients who had not lost Response through Week 54



Significant improvement in Quality of Life measures were seen in both the IBDQ and SF-36 (p<0.001) scores in infliximab-treated patients at week 30.

For patients receiving corticosteroids at baseline, the proportion of these patients in clinical remission and not receiving corticosteroids at week 30 was 31% (18 patients) for the 5mg/kg maintenance group and 37% (21 patients) for the 10 mg/kg maintenance group, compared with 11% (6 patients) in the placebo maintenance group (p=0.001 for both the 5mg/kg and 10 mg/kg maintenance groups). The median corticosteroid dose at baseline (20 mg/day) was reduced to 10 mg/day in the placebo maintenance group and 0 mg/day in the combined infliximab maintenance groups by week 30, indicating that at least 50% of the infliximab maintenance patients were able to discontinue steroid use.

In a subset of patients who participated in an endoscopic substudy, a significantly greater

proportion of patients in the infliximab maintenance groups combined (10/32 patients, 31%) had healing of the mucosa compared to patients in the placebo group (0/17 patients, 0%) at week 10 (p=0.010). Results were similar at week 54.

Fistulising Crohn's Disease

The safety and efficacy of infliximab were assessed in a randomised, double-blind, placebo-controlled study of 94 patients with fistulising Crohn's disease with fistulas that were of at least 3 months' duration. Thirty-one of these patients were treated with infliximab 5mg/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. Fifty-two (55%) had multiple cutaneously draining fistulas, 90% of patients had fistulas in the perianal area and 10% had abdominal fistulas.

Patients received 3 doses of infliximab 5 or 10 mg/kg or placebo at Weeks 0, 2 and 6 and 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 fistulas draining upon gentle compression, on at least two consecutive visits, without an increase in medication or surgery for Crohn's disease.

Sixty-eight percent (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 fistulas was achieved in 55% of infliximab-treated patients compared with 13% of placebo-treated patients (p=0.001).

The safety and efficacy of repeated infliximab infusions in patients with fistulising Crohn's disease were studied in a 1-year trial. A total of 306 patients received 3 doses of infliximab 5 mg/kg at week 0, 2 and 6. Among the randomised patients at baseline, 87% of the patients had perianal fistulas, 14% had abdominal fistulas, 9% had rectovaginal fistulas. The median CDAI score was 180. One-hundred and ninety-five patients responding to the 3 doses (for definition of response see description of primary endpoint for the trial above) were randomised at week 14 to receive either placebo or 5 mg/kg infliximab every 8 weeks through week 46. At week 14, 65% (177/273) of randomised patients were in fistula response. Patients randomised to infliximab maintenance had a significantly longer time to loss of fistula response compared to the placebo maintenance group (p<0.001). Median time to loss of response was >40 weeks in the infliximab group compared with 14 weeks in the placebo group. At week 54, 38% (33/87) of infliximab-treated patients had no draining fistulas compared with 22% (20/90) of placebo-treated patients (p=0.02). The infliximab group showed greater improvement in CDAI score from baseline compared with placebo (p=0.04). Patients who achieved a fistula response and subsequently lost response were eligible to receive infliximab maintenance therapy at a dose that was 5 mg/kg higher than the dose to which they were randomised. Of the placebo maintenance patients, 66% (25/38) responded to 5 mg/kg infliximab, and 57% (12/21) of infliximab maintenance patients responded to 10 mg/kg. Compared to placebo maintenance, patients on infliximab maintenance had a trend toward fewer hospitalisations. At week 30, greater improvement from baseline in IBDQ scores was seen in the infliximab maintenance group compared to placebo maintenance. Improvement in both scores was maintained through week 54.

Active Crohn's disease in children and adolescent patients (6 to 17 years)

The safety and efficacy of single and multiple doses of infliximab were assessed in a randomised, single-dose, multicentre Phase II study in 21 children and adolescent patients with active Crohn's disease, and in a randomised, multiple-dose, open-label, multicentre Phase III study in 112 children and adolescent Crohn's disease patients (the REACH trial). In REACH, all subjects 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).

In the Phase II single-dose trial of 21 patients (11 to 17 years old, median age 15.0 years), all patients achieved a clinical response (decrease in CDAI ≥ 70 points or decrease in PCDAI ≥ 10) at some point in the 20 weeks following the single dose of infliximab, and clinical remission (defined as a reduction in the modified CDAI score to below 150 points or a reduction in the PCDAI to below 10) was achieved by 10 (47.6%) patients. Of the 3 doses administered (1, 5, or 10 mg/kg), the 5 mg/kg and 10 mg/kg treatment groups had a larger proportion of patients achieving clinical remission (16.7% in the 1 mg/kg infliximab treatment group as compared with 57.1% and 62.5% in the 5 mg/kg and 10 mg/kg infliximab treatment groups, respectively). All 7 patients who had fistulising disease had their fistulas closed for at least 1 evaluation visit (8 weeks).

In the multiple-dose Phase III trial (REACH), 112 patients (6 to 17 years, median age 13.0 years) received 5 mg/kg infliximab at weeks 0, 2, and 6. Patients assessed by the investigator to be in clinical response at week 10 were randomised and received either 5 mg/kg infliximab 8-weekly or 12-weekly as a maintenance treatment regimen. If response was lost during maintenance treatment, crossing over to a higher dose or shorter dosing interval was allowed.

In REACH, clinical response at Week 10 was 88.4% (99/112) as compared with 66.7% (128/192) in adults (ACCENT 1). Similarly, the proportion of subjects achieving clinical remission at week 10 was 58.9% (66/112) as compared with 39.1% (75/192) in adults (ACCENT 1).

At week 30; the proportion of subjects in clinical response was significantly higher in the 8-weekly (73.1%, 38/52) than in the 12-weekly maintenance treatment group (47.1%, 24/51; p=0.007). At week 54, the proportion of subjects in clinical response was also significantly higher for subjects in the 8-weekly (63.5%, 33/52) than in the 12-weekly maintenance treatment group (33.3%, 17/51; p=0.002).

At week 30, the proportion of patients in clinical remission was significantly higher in the 8-weekly maintenance treatment group (59.6%, 31/52) than in the 12-weekly maintenance treatment group (35.3%, 18/51; p=0.013). At week 54, the proportion of patients in clinical remission was also significantly higher for patients in the 8-weekly (55.8%, 29/52) than in the 12-weekly (23.5%, 12/51; p<0.001) maintenance treatment groups.

In REACH, the change from baseline in average daily corticosteroid use was significant at weeks 10, 30, and 54 (p<0.001). For patients receiving corticosteroids at baseline in REACH, clinical remission achieved with no corticosteroids at week 30 was 45.8% for the 8-weekly and 33.3% for the 12-weekly maintenance treatment group. At week 54, 45.8% of patients in the 8-weekly and 16.7% of subjects in the 12-weekly maintenance treatment group were in clinical remission and not receiving corticosteroids.

Quality of Life (QOL) was assessed using the IMPACT III score (a QOL questionnaire

specifically developed and validated for paediatric patients with inflammatory bowel disease). It was administered only to subjects in North America. The mean changes (negative change indicates improvement) from baseline of the IMPACT III score at Weeks 10, 30 and 54 (-22.9, -21.1, and -24.3, respectively) were all significant ($p<0.001$).

The height z-score is a measure of the deviation of the paediatric patient's height from the expected height for a population of the same age and gender. In the population studied, the median z-score at baseline was –1.6. The median changes from baseline in the z-scores were 0.3 and 0.4 for week 30 and week 54, respectively. The z scores were significantly improved from baseline at both week 30 ($p<0.001$) and week 54 ($p<0.001$).

Ulcerative colitis

The safety and efficacy of infliximab were assessed in two (ACT 1 and ACT 2) randomised, 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-mercaptopurine (6-MP), azathioprine (AZA)]. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. In both studies, patients were randomised 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.

In both studies, clinical response and clinical remission were defined based on the Mayo score, which consists of four subscores: stool frequency, rectal bleeding, findings of endoscopy, and physician's global assessment. Each subscore is rated on a scale from 0 to 3, indicating normal (0) to severe (3) activity. The Mayo score is the sum of the 4 subscores. Clinical response was defined as a decrease from baseline in the Mayo score of ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1. Clinical remission was defined as a Mayo score ≤2 points, with no individual subscore >1.

In both ACT 1 and ACT 2 the primary endpoint was clinical response at Week 8. The major secondary endpoints were clinical response at Week 30, clinical remission at Week 8 and clinical remission at Week 30. The other major secondary endpoint was mucosal healing, which is defined as a Mayo endoscopy subscore of 0 or 1. Other efficacy endpoints include: corticosteroid endpoint (decrease in median daily corticosteroid dose from baseline to Week 30), sustained response (subjects in clinical response at both Week 8 and Week 30), sustained remission (subjects in clinical remission at both Week 8 and Week 30) and Quality of Life, as measured by the IBDQ, SF 36, and EQ-5D.

Table 13: Effects on clinical response, clinical remission and mucosal healing at Weeks 8 and 30. Combined data from ACT 1 & 2

	Placebo	**5 mg/kg**	**Infliximab 10 mg/kg**	**Combined**
Subjects randomised	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%
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%

	Placebo	5 mg/kg	Infliximab 10 mg/kg	Combined
Percentage of subjects in clinical remission, sustained remission, and in remission without corticosteroids				
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%
Randomised subjects with corticosteroids at baseline	139	130	139	269
Subjects without corticosteroids and in clinical remission at Week 30[b]	7.2%	21.5%	23.0%	22.3%
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 b: $p \leq 0.001$, for each infliximab treatment group vs. placebo				

In both studies, a significantly greater percentage of patients in the infliximab groups were in clinical response and clinical remission at week 8 when compared to placebo. Furthermore, in both ACT 1 and ACT 2, a significantly greater proportion of patients treated with 5 mg/kg or 10 mg/kg infliximab experienced clinical response and clinical remission at week 30 compared to placebo treatment. In addition, the proportion of patients in sustained response (i.e., were in clinical response at both week 8 and week 30) in the infliximab groups was at least twice as large as in the placebo group. Results from weeks 8 and 30 are shown in Table 13.

Of patients treated with corticosteroids at baseline, a significantly greater proportion of patients in the infliximab-treated groups were in clinical remission at week 30 and able to discontinue corticosteroids compared to the placebo-treated patients (22.3% versus 7.2%, respectively, see Table 13).

Additionally, at weeks 8 and 30, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg dose groups in ACT 1 and ACT 2 achieved mucosal healing compared to patients in the placebo group. The proportion of subjects with mucosal healing was similar between the 2 infliximab dose groups in the two studies (see Table 13).

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 a greater proportion of patients in the combined infliximab treatment group compared to the placebo treatment group at week 54 (34.6% 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 the placebo treatment group (37.9% vs. 14.0%, $p<0.001$; and 20.2% vs. 6.6%, $p<0.001$, respectively).

A greater proportion of patients in the combined infliximab treatment group were able to discontinue corticosteroids while remaining in clinical remission compared to the placebo

treatment group at both week 30 (22.3% vs. 7.2%, p ≤0.001, see Table 13) and week 54 (21.0% vs. 8.9%, p=0.022).

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 hospitalisations was 50% lower in the combined infliximab treatment group than in the placebo treatment group (9 versus 18 hospitalisations per 100 subjects, p=0.005). No notable differences were observed between the 5 mg/kg and 10 mg/kg infliximab treatment groups.

Paediatric Ulcerative Colitis (6 through 17 Years)

The efficacy and safety of induction and maintenance infliximab were assessed in a multicentre, randomised, open-label, parallel group clinical study (C0168T72) in 60 paediatric patients aged 6 through 17 years (median age 14.5 years) with moderately to severe active ulcerative colitis (Mayo score of 6 to 12; endoscopic subscore >2) with an inadequate response to conventional therapies. At baseline, 53% of patients were receiving aminosalicylates, 53% were receiving immunomodulator therapy (6-mercaptopurine (6-MP), azathioprine (AZA) and /or methotrexate (MTX)) and 62% of patients were receiving corticosteroids. Discontinuation of immunomodulators and corticosteroid taper were permitted after week 0. 77% of patients had extensive disease as indicated by endoscopy.

All patients received an induction regimen of 5 mg/kg infliximab at Weeks 0, 2, and 6. Patients who did not respond to infliximab at Week 8 (n=15) received no further drug and returned for safety follow-up. At week 8, 45 patients were randomised and received 5 mg/kg infliximab at either every 8 weeks or every 12 weeks as a maintenance treatment regimen.

The primary endpoint was clinical response at Week 8, defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, including a decrease in the rectal bleeding subscore by ≥ 1 points or achievement of a rectal bleeding subscore of 0 or 1. The proportion of patients in clinical response at week 8 was 73.3% (44/60). Clinical response at week 8 was similar between those with or without concomitant immunomodulator use at baseline.

Clinical remission at Week 8 was measured by the Mayo score, defined as a Mayo score of ≤2 points with no individual subscore >1. Clinical remission was also assessed at Week 8 and Week 54 using the Paediatric Ulcerative Colitis Activity Index (PUCAI) score and was defined by a PUCAI score of <10 points. Clinical remission at week 8 was 40% (24/60) as measured by the Mayo score and 33.3% (17/51) as measured by the PUCAI score.

At week 54, the proportion of patients in clinical remission as measured by the PUCAI score was 38% (8/21) in the every 8 weeks maintenance group and 18% (4/22) in the every 12 weeks 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 weeks and 0% (0/13) for the every 12 weeks maintenance treatment group.

Mucosal healing was defined as an endoscopy subscore (from the Mayo score) of 0 or 1. The proportion of patients with mucosal healing at week 8 was 68.3% (41/60) of which 33% (20/60) of patients achieved complete mucosal healing defined as having an endoscopy subscore of 0.

Although endoscopy was optional at week 54, 9 patients who had mucosal healing at week 8 had endoscopies at week 54. 89% (8/9) of these patients were still in mucosal healing.

IXIFI Clinical Study - Rheumatoid Arthritis

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

Study B5371002 was a multi-national, double-blind, randomised, comparative study to assess the efficacy and safety of IXIFI compared to Remicade® in adult subjects with moderately to severely active rheumatoid arthritis. 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-randomised to the IXIFI arm. At Week 54, all patients received open label IXIFI for an additional 24 weeks.

The study met its primary objective since the 95% confidence interval of the ACR20 response rate at Week 14 was within the pre-defined equivalence margin of (-13.5% to 13.5%). For the ACR20 primary endpoint in ITT population at Week 14, response rates were 62.7% for IXIFI and 64.1% for Remicade®.

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 suggested 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 suggested 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

In clinical trials in rheumatoid arthritis and Crohn’s disease patients, single dose intravenous infusions of 1, 3, 5, 10 or 20 mg/kg of infliximab yielded dose proportional increases in the maximum serum concentration (Cmax) and area under the concentration-time curve (AUC). The volume of distribution at steady state (median Vss of 3.0 to 4.1 litres) was not dependent

on the administered dose and indicated that infliximab is predominantly distributed within the vascular compartment. The elimination pathways for infliximab have not been characterised. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight or hepatic or renal function. Paediatric Crohn's patients in the 5 mg/kg and 10 mg/kg treatment groups had slightly higher serum concentrations after the initial infusion and slightly lower serum concentrations at later time periods (4 to 12 weeks) compared to adult Crohn's patients. No notable differences in single dose pharmacokinetic parameters and terminal half-life were observed between paediatric and adult Crohn's disease patients. The relatively small number of patients evaluated makes further detailed comparison difficult.

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

At single doses of 3 and 10 mg/kg in rheumatoid arthritis patients and 5 mg/kg in Crohn's disease patients, the median Cmax values were 77 and 277 μg/mL and 118 μg/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 a single infusion. Following the 3-dose regimen a slight accumulation of infliximab was observed in the serum after the second dose and no further clinically relevant accumulation thereafter. The proportion of patients who had undetectable infliximab concentrations at 8 weeks, after a maintenance infusion, was approximately 20%.

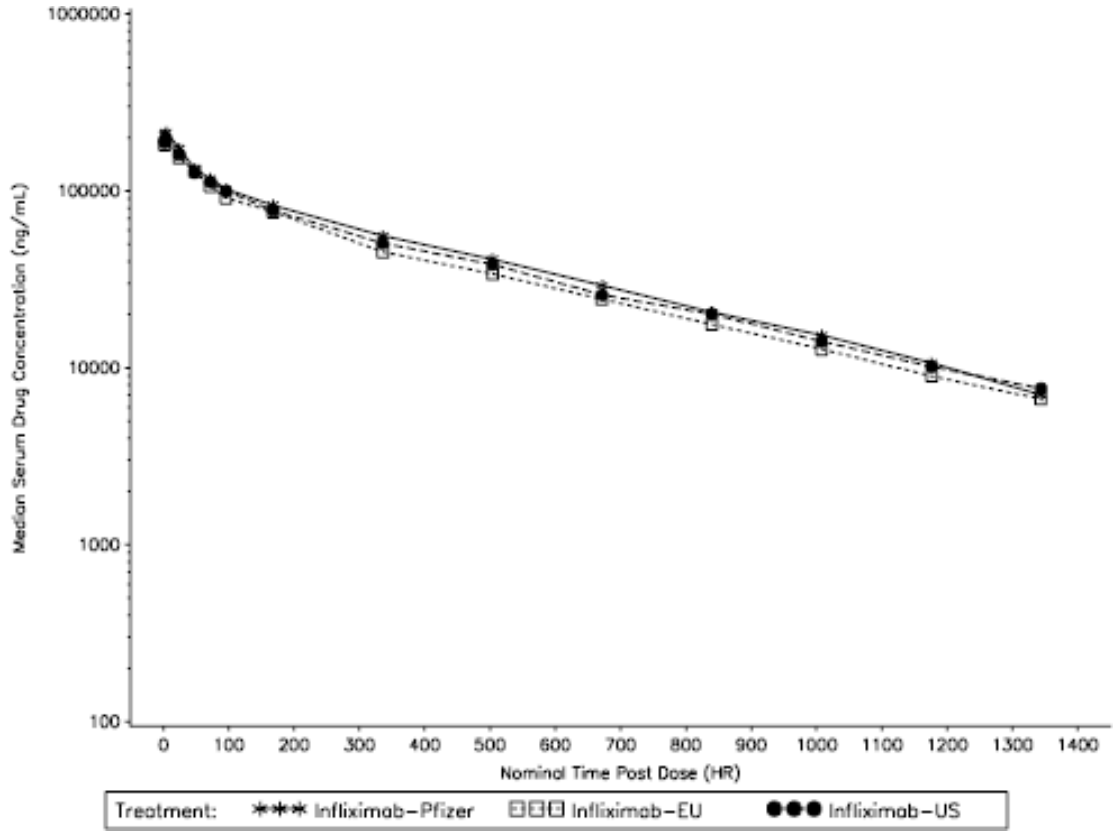
Limited pharmacokinetic studies of infliximab in psoriasis appear to show no significant differences to the pharmacokinetics in other indications.

IXIFI comparative pharmacokinetic studies

The PK similarity of IXIFI (PF-06438179, Infliximab Pfizer) and Remicade was evaluated in the clinical development program. Study B5371001 was a three-arm, double-blind, randomised (1:1:1), parallel-group, single-dose study that compared the PK of PF-06438179, 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 characterised 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 3. Median Serum Concentration-Time Profiles of PF-06438179, Infliximab-EU, and Infliximab-US Following a Single Intravenous 10 mg/kg Dose to Healthy Subjects in a semi-logarithmic scale



The arithmetic mean (±SD) PK parameters for infliximab-Pfizer, infliximab-EU, and infliximab-US are summarised in Table 14. 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 14. Arithmetic mean (±SD) pharmacokinetic parameter estimates of Infliximab-Pfizer, 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
$AUCT^a$ (µg•hr/mL)	$AUCT^a$ (µg•hr/mL)	51180 ± 12868	53010 ± 11906
AUC_{inf} (µg•hr/mL)	61460 ± 14386	57610 ± 14334	57610 ± 14334
CL (mL/hr/kg)	0.1725 ± 0.0456	0.1918 ± 0.0527	0.1855 ± 0.0521

Parameters (units)	IXIFI	Infliximab-EU	Infliximab-US
Vss (mL/kg)	79.58 ± 20.73	92.06 ± 25.85	84.92 ± 24.52
t½ (hr)	344.5 ± 99.72	367.6 ± 106.7	335.1 ± 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 t½ 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 PF-06438179 to infliximab-US, PF-06438179 to infliximab-EU, and infliximab-EU to infliximab-US. This study demonstrated the PK similarity of infliximab-Pfizer to both infliximab-US and infliximab-EU, and of infliximab-EU to infliximab-US.

Table 15. 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 Geometric Means[a]	90% CIs for Ratios
Parameters (units)	**Test**	**Reference**		
PF-06438179 (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
PF-06438179 (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	~~7.58~~ 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 PF-06438179 and infliximab-EU arms during treatment period 1 with contributions from subjects who differed in numbers over the assessment time points. The concentrations of serum PF-06438179 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 16. Serum PF-06438179 and Infliximab-EU concentrations, PK population – treatment period 1

	All Subjects		ADA-Positive Subjects		ADA-Negative Subjects	
Visit	PF-064381 79	Infliximab- EU	PF-064381 79	Infliximab- EU	PF-064381 79	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	N = 138 2846 (386-10050)	N = 141 2385 (192-7580)
Cmax (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)

	All Subjects		ADA-Positive Subjects		ADA-Negative Subjects	
Visit	PF-064381 79	Infliximab- EU	PF-064381 79	Infliximab- EU	PF-064381 79	Infliximab- EU
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 (5th - 95th percentile).
Abbreviations: ADA = anti-drug antibody; Cmax = 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 PF-06438179 in the RA patient population. This analysis identified covariates of body weight, sex and ADA titers as significant factors influencing infliximab-EU and PF-06438179 PK. Furthermore, results indicate that the PK of PF-06438179 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 PF-06438179, infliximab-US, and infliximab-EU.

5.3 Preclinical safety data

Genotoxicity

No genotoxic effects of infliximab were observed in assays for chromosomal damage (an assay performed using human lymphocytes and the *in vivo* micronucleus test) or gene mutations (Salmonella-Escherichia coli (Ames) assay).

Carcinogenicity

Long term studies in animals have not been performed to evaluate the carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium succinate hexahydrate

Succinic acid

Sucrose

Polysorbate 80

No preservatives are present.

6.2 Incompatibilities

No physical biochemical compatibility studies have been conducted to evaluate the

coadministration of IXIFI with other agents. IXIFI should not be infused concomitantly in the same intravenous line with other agents.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

IXIFI should be stored at 2°C to 8°C (Refrigerate. Do not Freeze).

Reconstituted Solution

The IXIFI reconstituted vial is biochemically and microbiologically stable for 18 hours at ambient temperatures (up to 30°C). However, since no preservative is present and to reduce microbiological hazard, use as soon as practicable after reconstitution.

Diluted Solution for Infusion

IXIFI infusion solution diluted in 0.9% sodium chloride is biochemically and microbiologically stable for 24 hours when stored between 2°C and 30°C, however, since no preservative is present, and to reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2-8°C for not more than 24 hours.

The product is for single use only and any unused portion of the solution should be discarded.

6.5 Nature and contents of container

Each vial contains 100 mg of infliximab in a 15 mL Type 1 clear glass vial with chlorobutyl stopper and crimp seal with flip-off cap.

After reconstitution with 10 mL Sterile Water for Injections, each mL contains 10 mg infliximab.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure

Infliximab is a chimeric IgG1 monoclonal antibody composed of human constant and murine variable regions, having an approximate molecular weight of 149,100 daltons. Infliximab is produced by recombinant cell line cultured by continuous perfusion and it is purified by a series of steps that includes measures to inactivate and remove viruses.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

TBC - Date of first inclusion in the ARTG.

10. DATE OF REVISION

TBC

Summary Table of Changes

Section changed	Summary of new information
NA	New Product Information document