Reminton

Instructions for infliximab for injection

Read all of this leaflet carefully and talk to your doctor before you start using this medicine.

Reminton (infliximab) for injection, for intravenous use
Initial Chinese Approval: 2021
Reminton (infliximab) is biosimilar to REMICADE (infliximab)

WARNING: SERIOUS INFECTIONS and MALIGNANCY

Infection

Increased risk of serious infections leading to hospitalization or death. The most of patients undergoing infections combine using immune inhibitors such as MTX and glucocorticoid.
Discontinue Reminton if a patient develops a serious infection.
The reported infections include the following types.
Active tuberculosis (TB): including the reactivation of latent tuberculosis. Patients with TB have frequently presented with disseminated or extrapulmonary diseases. Patients should be tested for latent TB before Reminton use and during treatment; if positive, start treatment for TB prior to starting Reminton.
Invasive fungal infections: including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis and pneumocystis. Patients histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. For some patients, antigen and antibody test result may be negative. Empiric antifungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
Infections due to bacteria, virus or other opportunistic pathogens: including legionella and listeria.
The risk and benefit of treatment with Reminton should be carefully considered piror to initiating therapy in patients with chronic or recurrent infection.
Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Reminton, including the possible development of tuberculosis in patients who tested negative for latent TB infection prior to initiating therapy.

Malignancies

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

Drug name
General name: infliximab for injection
Brand name: Reminton
English name: infliximab for injection
Chinese name: Zhusheyong Yingfulixi Dankang
Formula
API: infliximab
Excipients: sucrose, tween 80, sodium dihydrogen phosphate, disodium hydrogen phosphate
Character
This product is a white loose powder and colorless to pale yellow liquid with opalesce after dissolution.
No foreign matter.
Indication
Rheumatoid Arthritis (RA)
This is an anti-RA drug product for disease control in moderate to severe RA patients. This product can be in combination with methotrexate to reduce signs and symptoms and improve physical function to prevent disability.
Crohn's Disease (CD) in adult and children (NLT 6 years old)
For patients with moderately to severely active disease who have had an inadequate response to conventional therapy, this product can reduce signs and symptoms, induce and maintain clinical remission, induce the adult mucosal healing, improve life quality and decrease or stop adult using corticosteroid.
Fistula Crohn's Disease
For patients, this product can educe the number of enterocutaneous and rectovaginal fistulas, reduce signs and symptoms and improve life quality.
Ankylosing Spondylitis (AS)
For patients, this product can reduce signs and symptoms, including increase of range of motion, improve physical function and life quality.
Plaque Psoriasis (Ps)
This product is for treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies, such as methotrexate, cyclosporine and photochemotherapy, are medically less appropriate. This product can only be used when the doctor can monitor and interview the patients regularly.
Ulcerative Colitis (UC) in adult
This product is for treatment of adult patients with moderate to severe ulcerative colitis when other traditional therapies are medically less appropriate. This product can reduce signs and symptoms, induce and maintain clinical remission, induce the adult mucosal healing and decrease or stop using corticosteroid.
Strength
100mg/vial
Dosage and Administration
This product is administered by intravenous infusion.
Rheumatoid Arthritis: In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg every 8 weeks or treating as often as every 4 weeks.
Crohn's Disease: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg every 8 weeks if they later lose their response.
Pediatric Crohn's Disease (≥ 6 years old): 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.
Current available data does not support to continue using this product for treatment if there is no medical response in the first 10 weeks treatment period. For some patients, it may need a shorter administration interval to maintain the benefit from the treatment. For other patients, a longer administration interval may also have the benefit from the treatment. If dosage is increased to 5mg/kg at an 8 weeks interval, the risk of adverse reaction may increase. For those patients who do not benefit from the current standard treatment, it should be considered carefully to use an adjusted dosage. Because of absence of study data for pediatric patients NMT 6 years old, dosage and administration for these patients is unclear.
Ankylosing Spondylitis: 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.
Ankylosing Spondylitis palindromia: at a 20 weeks interval, the risk will increase for patients administrated with a single dose. Compared to the primary induced treatment, the effectiveness of product decrease but the mild to moderate infusion reaction increase.
The limited experience indicates that infusion reaction (including severe reaction) increase after palindromia. If the maintenance treatment is discontinued, restart of induced treatment is not recommended, but should administrate again based on maintenance treatment.
Plaque Psoriasis: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. If there is no response for patients after 14th week (after 4 doses administration), the treatment should be stopped.
Ulcerative Colitis: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.
Infusion reaction explanation: intravenous infusion should last for at least 2 hours with an in-line filter and patients should be observed for at least 1-2 hours after infusion to avoid acute infusion reaction. Hospital should be equipped with corticosteroid, epinephrine, antihistamines and artificial airway for first-aid.
According to judgment of doctor, patients can accept a pre-treatment with antihistamines, hydrocortisone or acetaminophen and decrease the infusion speed to decrease the risk of infusion reaction, especially for those patients who have underwent related infusion reaction.
During infusion, decrease the infusion speed or pause infusion to improve the mild to moderate infusion reaction. Once improvement, restart the infusion in a lower speed or administrate the antihistamines, acetaminophen or corticosteroid at the same time. If patients still cannot tolerate the infusion, it should be stopped.
For patients with severe hypersensitivity occurring during infusion or shortly after infusion, the treatment should be stopped. Handle the severe reaction based on the signs and symptoms by professional personnel and appropriate drug.
Guide for usage: the operation should be sterile.
1. 1.Calculate the dose, total volume of reconstituted product solution required and the number of product vials needed. More than one vial may be needed for a full dose.
2. Reconstitute each 100 mg vial with 10 mL of Sterile Water for Injection to obtain a concentration of 10 mg/mL, using a syringe equipped with a 21-gauge or smaller needle as follows:
•Remove the flip-top from the vial and wipe the top with an alcohol swab.
•Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder, which has a cake- like appearance. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual.
•Allow the reconstituted solution to stand for 5 minutes. Visually inspect the reconstituted solution for particulate matter and discoloration. The reconstituted solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if the lyophilized powder has not fully dissolved or if opaque particles, discoloration, or other foreign particles are present. Do not store unused reconstituted solution.
3. Dilute the total volume of the reconstituted product solution to 250 mL with sterile 0.9% Sodium Chloride Injection (do not dilute with any other diluent) as follows:
•Withdraw a volume from the 0.9% Sodium Chloride Injection 250 mL bottle or bag equal to the total volume of reconstituted product required for a dose. Slowly add the total volume of reconstituted product solution from the vial(s) to the 250 mL infusion bottle or bag.
•Discard any unused portion of the reconstituted product solution remaining in the vial(s).
•Gently invert the bag to mix the solution. The resulting infusion concentration should range between 0.4 mg/mL (minimum recommended concentration) and 4 mg/mL (maximum recommended concentration) of infliximab.
4. The infusion should begin within 3 hours of reconstitution and dilution. The infusion must be administered intravenously for at least 2 hours with an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 μm or less).
5. No physical biochemical compatibility studies have been conducted to evaluate the co- administration of product with other agents. Product should not be infused concomitantly in the same intravenous line with other agents.
For drug by parenteral administration, color change and particle should be confirmed by visual test at first.

Adverse reaction
From the clinical trial study report, most common drug adverse reactions (ADR) is upper respiratory infections and the incidence in test group and reference group is 25.3% and 16.5% respectively. The severe ADR caused by TNF inhibitor including infliximab includes reactivation of hepatitis B virus (HBV), congestive heart-failure (CHF), serious infection (including sepsis, tuberculosis and opportunistic infections), serum sickness (delayed hypersensitivity), blood system reaction, systemic lupus erythematosus or lupus like syndrome, demyelinating disease, liver and gall bladder event, lymphoma, hepatic splenic T cell lymphoma (HSTCL), leukemia, Merkel cell carcinoma, melanoma, childhood malignancy, nodule disease or sarcomatoid reaction, intestinal and perianal abscesses and severe infusion reaction.
The following table 1 list the ADR based on clinical trial and post-marketing experience (part of them are deadly case). ADR is divided into different groups based on systemic organ classification (SOC) and frequency: frequent (NLT 10%), normal 1%-10%), occasional (0.1%-1%), rare (0.01%-0.1%), very rare (<0.01%), unknown (cannot be evaluated based on available data). In each group, ADR is in the sequence of severity.

Table 1: Observed ADR in clinical trial and post-marketing experience

Infection	
Frequent	Virus infection (such as influenza, vesicular virus infection)
Normal	Bacterial infection (such as sepsis, cellulitis, abscess)
Occasional	Tuberculosis, fungal infection (such as candidiasis)
Rare	Meningitis, opportunistic infection [invasive infections with fungi (such as pneumocystosis, histoplasmosis, aspergillosis, coccidioidomycosis, cryptococcosis, blastomycosis), bacterial infection (such as atypical mycobacteriosis, listerellosis, salmonellosis), virus infection (such as cytomegalovirus)], parasitization reactivation of hepatitis B virus
Unknown	Vaccine breakthrough infection (after infliximab exposed in uterus)[1]
Malignant and nature undefined tumor (including cryptomere and polypus)	
Rare	Lymphoma, non-hodgkin lymphoma, hodgkin's disease, leukemia, melanoma, cervical cancer
Unknown	Hepatic splenic T cell lymphoma (mainly occur in young patients with CD and UC), Merkel cell carcinoma
Blood and lymphatic system	
Frequent	Neutropenia, leukopenia, anemia, lymphadenopathy
Occasional	Thrombocytopenia, lymphopenia, lymphocythemia
Rare	Agranulocytosis (including baby exposed to infliximab in uterus), thrombotic thrombocytopenic purpura, pancytopenia, hemolytic anemia, idiopathic thrombocytopenic purpura
Frequent	
Normal	Allergic respiratory symptoms
Occasional	Immediate hypersensitivity, lupus like syndrome, serum sickness or serum sickness like reaction
Rare	Rapid anaphylactic shock, vasculitis, sarcomatoid reaction
Mental disease	
Normal	Depression, insomnia
Occasional	Amnesia, mood swing, confusion, somnolence, psychentonia
Rare	Affective flattening
Nervous system	
Frequent	Headache
Normal	Dizzy, hypaesthesia, paresthesia
Occasional	Epilepsy, mental disease
Rare	Transverse myelitis, central nervous system demyelination disease (such as multiple sclerosis, optic neuritis), peripheral demyelination disease (such as Guillain-Barre Syndrome, multifocal motor neuropathy, chronic inflammatory demyelinating polyneuropathy)
Eye disease	
Normal	Conjunctivitis
Occasional	Keratitis, periorbital edema, hordeolum
Rare	Endoophthalmitis
Unknown	Temporary loss of vision during infusion or within 2h after infusion2, anterior ischemic optic neuropathy
Heart disease	
Normal	Tachycardia, palpitation
Occasional	Cardiac failure (kainogenesis or exacerbation), arrhythmia, syncope, bradycardia
Rare	Cyanosis, hydropericardium
Unknown	Myocardial ischemia or myocardial infarction within 24h after beginning infusion
Blood vessels and lymphatics disease	
Normal	Hypotension, hypertension, ecchymosis, hectic fever, flush
Occasional	Peripheral ischemia, thrombophlebitis, hematoma
Rare	Loop failure, petechial, vasospasm
Respiratory system	
Frequent	Upper respiratory infection, nasosinusitis
Normal	Lower respiratory infection (such as bronchitis, pneumonia), breathing difficulties, epistaxis
Occasional	Pulmonary edema, bronchospasm, pleurisy, pleural effusion
Rare	Interstitial Lung Disease (such as pulmonary fibrosis, pneumonia and progressive disease)
Gastrointestinal system	
Frequent	Stomachache, nausea
Normal	Gastrointestinal bleeding, diarrhea, indigestion, gastroesophageal reflux, constipation, emesis
Occasional	Enterobrosis, enterostenosis, pancreatitis, cheilitis, diverticulitis
Unknown	Ileus
Hepatic and gall diseases	
Normal	Abnormal liver function, transaminase goes up
Occasional	Hepatitis, hepatocellular damage, cholecystitis
Rare	Autoimmune hepatitis, icterus
Unknown	Hepatic failure
Skin and subcutaneous tissue	
Normal	Psoriasis (kainogenesis or exacerbation), including pustules type psoriasis (mainly on palm and sole of the foot), urticarial, rash, skin itch, hidrosis, dry skin, mycotic dermatitis, eczema, baldness
Occasional	Bullous eruption, onychomycosis, seborrhagia, acne rosacea, cutaneous papillomatosis, hyperkeratosis, abnormal skin pigmentation
Rare	Toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, linear IgA bullous dermatoses, acute generalized
	exanthematous pustulosis, moss like reaction
Unknown	Dermatomyositis exacerbation
Musculoskeletal and connective tissue	
Normal	Arthralgia, myalgia, backache
Kidney and urinary system	
Normal	Urinary tract infection
Occasional	Nephropyelitis
Reproductive system and breast	
Occasional	Colpitis
Systemic disease and reaction in administration site	
Frequent	Infusion reaction, pain
Normal	Chest pain, fatigued, fever, reaction in administration site, edema, shiver
Occasional	Delayed union
Rare	Granulomatous lesions
Examination	
Occasional	Autoantibody positive
Rare	Abnormal complement factor

Remark 1: include perlsucht, please refer to chapter "warning"
Remark 2: in a Chinese clinical trial, one patient with UC is reported to occur moderate ischemic optic neuropathy and it does not recover. The relativity with infliximab is not clear.

Infusion reaction
An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion. In the phase III clinical studies, approximately 18% of infliximab-treated patients experienced an infusion reaction compared with 5% of placebo- treated patients. Of infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period.
Among all INFLIXIMAB infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued INFLIXIMAB because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. INFLIXIMAB infusions beyond the initial infusion were not associated with a higher incidence of reactions. The infusion reaction rates remained stable in Ps through 1 year in Ps Study I. In psoriasis Study II, the rates were variable over time and somewhat higher following the final infusion than after the initial infusion. Across the 3 Ps studies, the percent of total infusions resulting in infusion reactions (i.e., an adverse event occurring within 1 hour) was 7% in the 3 mg/kg group, 4% in the 5 mg/kg group, and 1% in the placebo group.
Patients who became positive for antibodies to infliximab were more likely (approximately two-to three-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of both antibodies to infliximab and infusion reactions.
In a RA clinical trial (ASPIRE), the first three infusion time is more than 2h. For patients who do not have infusion reaction, the infusion time can be shortened but NLT 40min. In this trial, 66% (686/1040) patients accept at least one time infusion of which time is NMT 90min. 44% (454 /1040) patients accept at least one time infusion of which time is NMT 60min. 15% patients (74/494) who at least undergo one rapid infusion have infusion reaction. 0.4% patients (2/494) have a severe infusion reaction. Until now, the rapid infusion study has not been conducted for dosage more than 6mg/kg.
In a CD clinical trial (SONIC), the infusion reaction incidence for patients treated with infliximab only is 16.6% (27/163). The infusion reaction incidence for patients treated with combination of infliximab and azathioprine and azathioprine only is 5% (9/179) and 5.6% (9/161) respectively. One patient has severe infusion reaction in the infliximab treatment group (<1%).
In the post-marketing PV, such immediate hypersensitivity case related to use of infliximab is reported. The hypersensitivity includes laryngeal edema, severe bronchospasm and convulsions. During the infusion or within 2h after infusion, temporary loss of vision case has been reported. Within 24h after beginning infusion, cerebrovascular accident, myocardial ischemia or myocardial infarction (some are deadly) and arrhythmia case has been reported.

Infusion Reactions Following Re-administration
In the RA, CD, Ps clinical trial, re-administration after drug withdrawal for a time can result in a higher rate of infusion reaction than maintenance treatment.
In a clinical trial of patients with moderate to severe Ps designed to assess the efficacy of long term maintenance therapy versus re-treatment with an induction regimen of INFLIXIMAB following disease flare, 4% (8/219) of patients in the re-treatment induction therapy arm experienced serious infusion reactions versus <1% (1/222) in the maintenance therapy arm. Patients enrolled in this trial did not receive any concomitant immunosuppressant therapy. In this study, the majority of serious infusion reactions occurred during the second infusion at Week 2. Symptoms included, but were not limited to, dyspnea, urticaria, facial edema, and hypotension. In all cases, INFLIXIMAB treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed hypersensitivity
Delayed hypersensitivity is rare in the clinical trial and mainly occur in the patients whose the drug withdraw time is NMT 1 year. In Ps studies, approximately 1% of INFLIXIMAB-treated patients experienced a possible delayed hypersensitivity reaction in the early treatment, generally reported as serum sickness or a combination of arthralgia and/or myalgia with fever and/or rash. Some patients also has symptoms of skin itch, face, hand or lip edema, headache, sore throat, urticarial and dysphagia.
There is no enough data to report the incidence of delayed hypersensitivity after drug withdraw for more than 1 year. However, the limited clinical trial indicates that the risk of delayed hypersensitivity increase along with the prolonging of drug withdraw.
In a one year clinical trial, incidence of serum sickness for CD patients administrated with repeated infusion (ACCENT I) is 2.4%.

Immunogenicity
There is potential for occurrence of anti-drug antibody (ADA) when treatment with infliximab. The detection of ADA in patients sample will be influenced by existence of infliximab in the serum so that the ADA percent is underestimated.
The incidence of antibodies to infliximab in patients with RA and CD given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through 1 to 2 years of INFLIXIMAB treatment. A higher incidence of antibodies to infliximab was observed in CD patients receiving INFLIXIMAB after drug-free intervals >16 weeks. In a PsA study in which 191 patients received 5 mg/kg with or without MTX, antibodies to infliximab occurred in 15% of patients. The majority of antibody-positive patients had low titers. Antibody development was lower among RA and CD patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX. Patients who were antibody-positive were more likely to have higher rates of clearance, have reduced efficacy, and to experience an infusion reaction than were patients who were antibody negative.
In the Ps Study II, which included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 36% of patients treated with 5 mg/kg every 8 weeks for 1 year, and in 51% of patients treated with 3 mg/kg every 8 weeks for 1 year.
In the Ps Study III, which also included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 20% of patients treated with 5 mg/kg induction (weeks 0, 2 and 6), and in 27% of patients treated with 3 mg/kg induction. Despite the increase in antibody formation, the infusion reaction rates in Studies I and II in patients treated with 5 mg/kg induction followed by every 8 week maintenance for 1 year and in Study III in patients treated with 5 mg/kg induction (14.1%-23.0%) and serious infusion reaction rates (<1%) were similar to those observed in other study populations. The clinical significance of apparent increased immunogenicity on efficacy and infusion reactions in Ps patients as compared to patients with other diseases treated with INFLIXIMAB over the long term is not known.

Infection
Tuberculosis (TB), sepsis and pneumonia induced by bacterial infection, invasive infections with fungi, virus infection and other opportunistic infection was observed in patients who are treated with infliximab. Part of these infections are deadly. The normal opportunistic infection of which death rate is more than 5% includes pneumocystosis, candidiasis, listerellosis and aspergillosis.
In INFLIXIMAB clinical studies, treated infections were reported in 36% of INFLIXIMAB- treated patients and in 25% of placebo-treated patients.
In RA clinical trial, the incidence of serious infection rate in the combination treatment (infliximab and MTX) group is higher than MTX treatment group and it is more obvious when dosage reach to or more than 6mg/kg.
In the volunteer AE report after marketing, the normal SAE is infection and part of these infections are deadly. Almost 50% of death report is related to infection. The reported TB includes extra pulmonary tuberculosis and miliary tuberculosis.

Hepatotoxicity
Icterus and noninfectious hepatitis (some has character of autoimmune hepatitis) has been reported in patients receiving INFLIXIMAB.
In clinical trials, mild to moderate elevations of glutamic-pyruvic transaminase (ALT) and glutamic oxalacetic transaminase (AST) were observed in patients treated with infliximab. However, there is no severe liver injury. ALT increase to the 5 times of upper limit of normal range (please refer to table 2). ALT elevation is more common than AST in a greater proportion of patients receiving infliximab than in controls (table 2) both when INFLIXIMAB was given as monotherapy and when it was used in combination with other immunosuppressive agents. For most patients, the transaminase abnormalities is temporary but for some patients it last for a longer timer. 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 2: Proportion of Patients with Elevated ALT in Clinical Trials

	Proportion of patients with elevated ALT					
	>1 to <3 × ULN		≥3 × ULN		≥5 × ULN	
	Placebo	INFLIXIMAB	Placebo	INFLIXIMAB	Placebo	INFLIXIMAB
Rheumatoid arthritis[1]	24.0%	34.4%	3.2%	3.9%	0.8%	0.9%
Crohn's disease[2]	24.1%	34.9%	2.2%	4.9%	0.0%	1.5%
Pediatric Crohn's disease[3]	NA	18.2%	NA	4.4%	NA	1.5%
Ulcerative colitis[4]	12.4%	17.4%	1.2%	2.5%	0.4%	0.6%
Pediatric Ulcerative colitis[5]	NA	16.7%	NA	6.7%	NA	1.7%
Ankylosig spondylitis[6]	14.5%	51.1%	0.0%	9.5%	0.0%	3.6%
Psoriatic arthritis	16.3%	49.5%	0.0%	6.8%	0.0%	2.1%
Plaque psoriasis[7]	50.1%	23.8%	0.7%	7.7%	0.0%	3.4%

Remark 1: Placebo patients received methotrexate while INFLIXIMAB patients received both INFLIXIMAB and methotrexate. Median follow-up was 58 weeks.
Remark 2: Placebo patients in the 2 Phase 3 trials (trial code C0168T21 and C0168T26) in CD received an initial dose of 5 mg/kg INFLIXIMAB at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to INFLIXIMAB are included in the INFLIXIMAB group in ALT analysis. In another Phase 3 trial (trial code C0168T67) in CD received placebo and 2.5mg/kg azathioprine in the maintenance phase.
Remark 3: Patients were from the T23, T55 and T47 clinical trial of which indication is paediatric CD. Median follow-up was 53 weeks.
Remark 4: Patients were from the C0168T37 and C0168T46 clinical trial of which indication is UC. Specifically, the median duration of follow-up was 30 weeks for placebo and 31 weeks for INFLIXIMAB.
Remark 5: Data were from C0168T72 clinical trial.
Remark 6: Data were from C0168T51 clinical trial.
Remark 7: ALT values are obtained in 2 Phase 3 Ps studies (trial code C0168T38 and C0168T44).

Malignancies and lymphoproliferatire diseases
In the clinical trials, 5 subjects with lymphoma and 26 subjects with other kinds of malignancies were discovered in 5780 subjects (including 5494 patients) of infliximab group, but only 1 subject with malignancies was discovered in 1600 subjects (including 941 patients) of placebo group.
In a long-term safety study (5 years) of infliximab, 5 subjects with lymphoma and 38 subjects with other kinds of malignancies were discovered in 3210 subjects.
In a randomized controlled clinical trial exploring the use of INFLIXIMAB in patients with moderate to severe COPD who were either current smokers or ex-smokers, patients were treated with INFLIXIMAB at doses similar to those used in RA and CD. Of these INFLIXIMAB-treated patients, 9 developed a malignancy, including 1 lymphoma, for a rate of 5.7% (median duration of follow-up 0.8 years; 95% CI 2.65% - 10.6%). There was 1 reported malignancy among 77 control patients for a rate of 1. 3% (median duration of follow-up 0.8 years; 95% CI 0.03% – 7.0%). The majority of the malignancies developed in the lung or head and neck. A population-based retrospective cohort study found an increase in the incidence of invasive cervical cancer in women with RA treated with INFLIXIMAB compared to biologics-naïve patients or the general population, particularly those over 60 years of age.
Furthermore, based on the post-marketing report after infliximab treatment, hepatic splenic T cell lymphoma mainly occurred in patients with CD or UC, particular those young man.

Antinuclear antibody (ANA)/ Anti double strands DNA (dsDNA) antibody
Approximately half of INFLIXIMAB-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately 17% of INFLIXIMAB-treated patients compared with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

Congestive heart-failure (CHF)
In a randomized, double-blind study evaluating INFLIXIMAB in moderate or severe heart failure (NYHA Class III/IV; left ventricular ejection fraction ≤35%), 150 patients were randomized to receive treatment with 3 infusions of INFLIXIMAB 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg INFLIXIMAB dose. At 1 year, 8 patients in the 10 mg/kg INFLIXIMAB group had died compared with 4 deaths each in the 5 mg/kg INFLIXIMAB and the placebo groups. There were trends toward increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg INFLIXIMAB treatment groups, versus placebo. INFLIXIMAB has not been studied in patients with mild heart failure (NYHA Class I/II)
Based on post-marketing experience, there were some aggravating heart failure cases reported for patients treated with infliximab (no matter with or without obvious induction factor). And there were some incipient heart failure cases reported for patients (including those patients without forepassed cardiovascular disease), especially some patients NMT 50 years old.

ADR in paediatric CD treatment
Generally, the frequency and type of ADR occurred in paediatric CD patients and adult CD patients were similar. The next paragraph describe the difference and the specific events that should be considered.
In a random trial, 103 patients with paediatric CD were treated with 5mg/kg infliximab (until 54 weeks). The frequency of ADR higher than that of 385 patients with CD in a similar trial included: anemia (10.7%), hemafecia (9.7%), leukopenia (8.7%), flushing (8.7%), virus infection (7.8%), neutropenia (6.8%), fracture (6.8%), bacterial infection (5.8%) and respiratory allergic reaction (5.8%).
In REACH study, 56.3% random grouped patients reported infection. The frequency of report for patients with a maintenance administration every 8 weeks was higher than that of every 12 weeks (73.6% and 38.0%). 3 patients and 4 patients in 8 weeks group and 12 weeks group reported serious infection. The most common infection was upper respiratory infection and pharyngitis. The most common serious infection was abscess. Totally 3 patients reported pneumonia in which 2 patients were from 8 weeks group and another from 12 weeks group. 2 patients from 8 weeks group reported herpes zoster. In ACCENT I study, 50.3% patients treated with 5mg/kg infliximab reported infection.
In general, in REACH study, 17.5% random grouped patients reported 1 or more times infusion reaction (17.0% in 8 weeks group and 18.0% in 12 weeks group). No severe infusion reaction was observed, but non-severe immediate allergic reaction occurred in 2 patients.
3 paediatric patients (2.9%) were anti-drug antibody positive.

Gerontal patient (NLT 65 years old)
The incidence of serious infections in INFLIXIMAB-treated geriatric patients was 11.3% which was greater than in INFLIXIMAB-treated younger adult patients (4.6%). The incidence of serious infections in MTX-treated geriatric patients was 5.2% which was greater than in MTX-treated younger adult patients (2.7%).

Post-marketing experience
After marketing, ADR of infliximab were reported in paediatric and adult patients. Since these reports were volunteer submitted and sample size was not confirmed, the incidence and relativity with infliximab was unknown.
After marketing, following ADR were reported, even including some death cases: agranulocytosis (including baby exposed to infliximab in uterus), Interstitial Lung Disease (including pulmonary fibrosis, interstitial pneumonia and rapidly progressive disease), idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, hydropericardium, systemic and cutaneous vasculitis, erythema multiforme, stevens Johnson syndrome, toxic epidermal necrosis dissolved, peripheral demyelination (such as Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy), stroke within 24h after beginning infliximab infusion, new or aggravating psoriasis (including all pustular subtypes, mainly in palmoplantar), transverse myelitis and neuropathy (other neuropathy reaction was observed), acute liver failure, icterus, hepatitis, cholestasis, serious infection, protozoan infection, (after exposure to infliximab in uterus) infection outbreak caused by vaccine injection (including prapes caused by diffuse BCG vaccine infection) and malignancies (including melanoma, cervical cancer and Merkel cell carcinoma).
For pediatric use, the most common severe adverse event was infection (some were deadly), including opportunistic infections, tuberculosis, infusion reaction and hypersensitivity. Spontaneous adverse events included malignancies, temporary liver enzymes abnormal, lupus-like syndrome spontaneous antibody positive.

There were patient cases, who were treated with infliximab, reported to occur hepatic splenic T cell lymphoma. Most cases were occurred on main young male patients with CD and UC. Haemophilic lymphohistiocytic proliferation was rarely reported.
The infusion related reaction: after marketing, hypersensitivity including throat swelling, epilepsy and severe bronchospasm were reported.
During infliximab infusion or within 2h after infusion, there was a case reporting temporary loss of vision.
There was a case reporting myocardial ischemia/myocardial infarction or arrhythmia within 24h after infusion.

Contraindication
The use of INFLIXIMAB is contraindicated in patients with moderate or severe heart failure (NYHA Class III/IV).
INFLIXIMAB is contraindicated in patients with a previous severe hypersensitivity reaction to infliximab or any of the inactive ingredients of INFLIXIMAB or any murine proteins.
INFLIXIMAB is contraindicated in patients with a tuberculosis or other active infection (including opportunistic infections, sepsis and abscess)

Warning and precautions
Serious infection
Patients treated with infliximab are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.
Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, salmonellosis andntuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.
Treatment with infliximab should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:
- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis;
- with underlying conditions that may predispose them to infection.

Tuberculosis
Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving INFLIXIMAB, including patients who have previously received treatment for latent or active tuberculosis. Cases of active tuberculosis have also occurred in patients being treated with INFLIXIMAB during treatment for latent tuberculosis.
Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating INFLIXIMAB and periodically during therapy. The evaluation should include the detailed medical history of patients such as tuberculosis history, history of previous intimate contact with tuberculosis patients and previous and current tuberculosis treatment regimen. Screening should be conducted for all patients, including chest imaging (chest CT was recommended) and tuberculin test. If appropriate, mycobacterium tuberculosis antigen-specificity T cell enzyme-linked immune-spot assay was recommended. If make a definite diagnosis that patients were with active tuberculosis, treatment with infliximab is forbidden.
If patients were doubted with latent tuberculosis patient should consult the local professional healthcare provider. Anti-tuberculosis therapy should be conducted prior to initiation of INFLIXIMAB in patients.
Treatment of latent tuberculosis infection prior to therapy with TNF blockers has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating INFLIXIMAB, even for patients previously vaccinated with Bacille Calmette-Guérin (BCG). Here remind the prescribers that there is a risk of false negative test result of tuberculin skin testing, especially for those patients with serious disease or hypoimmunity.
Anti-tuberculosis therapy should also be considered prior to initiation of INFLIXIMAB in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti- tuberculosis therapy is appropriate for an individual patient.
Tuberculosis should be strongly considered in patients who develop a new infection during INFLIXIMAB treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis. Patients should be informed to ask medical help if tuberculosis symptom (continuous cough, weight decrease, low-grade fever) occur during or after treatment.

Monitor
Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with INFLIXIMAB, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with INFLIXIMAB.
Tuberculosis risk should be evaluated regularly during treatment and take care of extra pulmonary tuberculosis and fowl tuberculosis.
INFLIXIMAB should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with INFLIXIMAB should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

Invasive fungal infection
For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

Malignancies
Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF blockers (initiation of therapy ≤18 years of age), including INFLIXIMAB. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post- marketing and are derived from a variety of sources, including registries and spontaneous post-marketing reports.
Lymphomas
In the controlled portions of clinical trials of all the TNF blockers, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of INFLIXIMAB clinical trials, 5 patients developed lymphomas among 5707 patients treated with INFLIXIMAB (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In RA patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for RA, CD, PsA, AS, UC, and Ps, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population. Patients with CD, RA or Ps, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Cases of acute and chronic leukemia have been reported with postmarketing TNF blocker use in RA and other diseases. Even in the absence of TNF blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Paediatric malignancies
Malignancies, some fatal, have been reported among children, adolescents and young adults (NMT 22 years old) who received treatment with TNF blockers (initiation of therapy ≤18 years of age), including INFLIXIMAB for CD, juvenile idiopathic arthritis (JIA) or other disease treatment. Approximately half of these cases were lymphomas and the other cases represented a variety of malignancies, including rare malignancies that are not usually observed in children and adolescents. For most patients, combination treatment with immunosuppressants, such as MTX, azathioprine or 6- mercaptopurine, is taken. The effect of THF inhibitor in malignancies development for children and adolescents is still unknown.

Hepatosplenic T-cell lymphoma (HSTCL)
Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including INFLIXIMAB. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. The majority of reported INFLIXIMAB cases have occurred in patients with CD or UC and most were in adolescent and young adult males. It is uncertain whether the occurrence of HSTCL is related to TNF blockers or TNF blockers in combination with these other immunosuppressants. When treating patients, consideration of whether to use INFLIXIMAB alone or in combination with other immunosuppressants such as azathioprine or 6-mercaptopurine should take into account a possibility that there is a higher risk of HSTCL with combination therapy versus an observed increased risk of immunogenicity and hypersensitivity reactions with INFLIXIMAB monotherapy from the clinical trial data.

Skin cancer
Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including INFLIXIMAB. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Cervical cancer
A population-based retrospective cohort study using data from Swedish national health registries found a 2 to 3 fold increase in the incidence of invasive cervical cancer in women with RA treated with INFLIXIMAB compared to biologics-naïve patients or the general population, particularly 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.

Other malignancies
In the controlled portions of clinical trials of some TNF blockers including INFLIXIMAB, more malignancies (excluding lymphoma and non-melanoma skin cancer [NMSC]) have been observed in patients receiving those TNF blockers compared with control patients. During the controlled portions of INFLIXIMAB trials in patients with moderately to severely active RA, CD, PsA, AS, UC, and Ps, 14 patients were diagnosed with malignancies (excluding lymphoma and NMSC) among 4019 INFLIXIMAB-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among INFLIXIMAB-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for INFLIXIMAB-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among INFLIXIMAB-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.
In a clinical trial exploring the use of INFLIXIMAB in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in INFLIXIMAB-treated patients compared with control patients. All patients had a history of heavy smoking. Prescribers should be cautious to use infliximab in patients with moderate to severe COPD.
Prescribers should exercise caution when considering the use of INFLIXIMAB in patients with moderate to severe COPD.
Ps patients should be monitored for non-melanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for INFLIXIMAB, NMSCs were more common in patients with previous phototherapy
The potential role of TNF blockers in the development of malignancies is not known. Rates in clinical trials for INFLIXIMAB cannot be compared to rates in clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering INFLIXIMAB treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving INFLIXIMAB.
For patients with ulcerative colitis combined with an increased risk of colon dysplasia or colon cancer, or a medical history of colon dysplasia or colon cancer, screening for dysplasia should be conducted before and during the treatment. This evaluation should include coloscope and biopsy. Since the possibility of increased cancer risk for patients with new dysplasia caused by infliximab treatment is not established, caution should be taken to evaluate the risk and benefit for individual patient and consider stopping the treatment.

Hepatitis B virus reactivation
Use of TNF blockers, including INFLIXIMAB, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus (such as surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation.
Patients should be tested for HBV infection before initiating TNF blocker therapy, 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. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF blocker therapy in this situation and monitor patients closely.

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

Heart failure
The use of INFLIXIMAB is normally contraindicated in patients with heart failure because of adverse reaction. Only when other theories are not available, infliximab can be used. A randomized, double-blind, placebo-controlled study evaluated the use of INFLIXIMAB (5 mg/kg or 10 mg/kg at Weeks 0, 2, and 6) in patients with moderate or severe heart failure [New York Heart Association (NYHA) Functional Class III/IV]. Compared to patients who received placebo, there was a higher rate of mortality and a higher risk of hospitalization at Week 28 due to heart failure in patients who received the 10 mg/kg INFLIXIMAB dose, and higher rates of cardiovascular adverse events in patients who received INFLIXIMAB doses of 5 mg/kg and 10 mg/kg.
There have been post-marketing reports of new onset and worsening heart failure, with and without identifiable precipitating factors (e.g., pre-existing cardiovascular disease), in INFLIXIMAB-treated patients. Some of these patients have been under 50 years of age.
If a decision is made to administer INFLIXIMAB (≤ 5 mg/kg) to patients with moderate or severe heart failure or to administer INFLIXIMAB (any approved dose) to patients with mild heart failure, they should be closely monitored during therapy, and INFLIXIMAB should be discontinued if new or worsening symptoms of heart failure appear.

Infusion reaction/ hypersensitivity reaction
INFLIXIMAB has been associated with hypersensitivity reactions (including anaphylactic shock and delayed hypersensitivity) that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions (including anaphylaxis, urticaria, dyspnea, and/or hypotension), have occurred during or within 2 hours of INFLIXIMAB infusion.
However, in some cases, serum sickness-like reactions have been observed in patients after initial INFLIXIMAB therapy (i.e., as early as after the second dose), and when INFLIXIMAB therapy was reinstituted following an extended period without INFLIXIMAB treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with a marked increase in antibodies to infliximab, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy.
INFLIXIMAB should be discontinued for severe hypersensitivity reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction.
In RA, CD and Ps clinical trials, re-administration of INFLIXIMAB after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment [see Adverse Reactions (6.1)]. In general, the benefit-risk of re-administration of INFLIXIMAB after a period of no-treatment, especially as a re-induction regimen given at weeks 0, 2 and 6, should be carefully considered. In the case where INFLIXIMAB maintenance therapy for Ps is interrupted, INFLIXIMAB should be reinitiated as a single dose followed by maintenance therapy.

Autoimmunity
Treatment with INFLIXIMAB may result in the formation of autoantibodies and in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus- like syndrome following treatment with INFLIXIMAB, treatment should be discontinued.

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

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

Administration with abatacept
In clinical studies, concurrent administration of TNF blockers and abatacept have been associated with an increased risk of infections including serious infections compared with TNF blockers alone, without increased clinical benefit. Therefore, the concurrent use of INFLIXIMAB and abatacept is not recommended.

Administration with other biological products
There is insufficient information regarding the concurrent use of INFLIXIMAB with other biological products used to treat the same conditions as INFLIXIMAB. The concurrent use of INFLIXIMAB with these biological products is not recommended because of the possibility of an increased risk of infection.

Switching between biological disease-modifying antirheumatic drugs
Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection. If replacement is necessary, it should continue to monitor the infection of patients.

Hematologic reaction
Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving INFLIXIMAB. The causal relationship to INFLIXIMAB therapy remains unclear. Although no high-risk group(s) has been identified, concurrent use of INFLIXIMAB and anakinra is not recommended.

Administration with abatacept
In clinical studies, concurrent administration of TNF blockers and abatacept have been associated with an increased risk of infections including serious infections compared with TNF blockers alone, without increased clinical benefit. Therefore, the concurrent use of INFLIXIMAB and abatacept is not recommended.

Administration with other biological products
There is insufficient information regarding the concurrent use of INFLIXIMAB with other biological products used to treat the same conditions as INFLIXIMAB. The concurrent use of INFLIXIMAB with these biological products is not recommended because of the possibility of an increased risk of infection.

Switching between biological disease-modifying antirheumatic drugs
Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection. If replacement is necessary, it should continue to monitor the infection of patients.

Hematologic reaction
Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving 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 hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on INFLIXIMAB. Discontinuation of INFLIXIMAB therapy should be considered in patients who develop significant hematologic abnormalities.

Vaccinations and use of live vaccines/therapeutic infectious agents
In patients receiving TNF blockers, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines can result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with INFLIXIMAB is not recommended. Female patients who received infliximab during the gestation should be cautious to vaccination to her infant because infliximab is known to cross the placenta and has been detected up to 12 months following birth.
Fatal outcome due to disseminated BCG infection has been reported in an infant who received a BCG vaccine after in utero exposure to infliximab. At least a 12 month waiting period following birth is recommended before the administration of any live vaccine to infants exposed in utero to infliximab, unless infliximab is not detected or the benefit of vaccination (such as BCG, rotavirus vaccine, oral polio attenuated live vaccine, live attenuated measles and rubella vaccine, japanese encephalitis vaccine) obviously more than risk. It is recommended to evaluate the risk and benefit of infant receiving vaccination during the treatment of gestation period.
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. It is recommended that before administration with infliximab, inject all necessary vaccines in advance. The interval of vaccination and infliximab treatment should be based on current guidance of vaccination.

Other
The safety data is limited for a synchronous surgery (including arthroplasty) treatment. If plan a surgery, the long half-life of infliximab should be considered. After surgery, monitor the infection of patients closely and take appropriate actions.
Ineffective in CD treatment may indicate that the patients are with stubborn fibrostenosis and surgery may be planed. There is no data indicating infliximab will cause fibrostenosis or make it worsen.

Pregnancy and lactation
Fertile woman
Fertile woman should volunteer to take effective contraceptives at least until 6 months after final administration of infliximab.

Gestation woman
Available observational studies in pregnant women exposed to INFLIXIMAB (about 450 patients), in which about 230 patients were exposed to infliximab in early gestation stage, showed no increased risk for gestation. However, findings on other birth and maternal outcomes were not consistent across studies of different study design and conduct (see Data). Because of the inhibition to TNFα, administrate infliximab during gestation have effect in infant normal immune response. An embryofetal development study was conducted in pregnant mice, an analogous antibody that selectively inhibits the functional activity of mouse TNFα. No maternal toxicity or adverse developmental effects in offspring were observed.
Because of limited clinical experience, it cannot exclude the risk of infliximab administration during gestation. So gestation woman is not recommended to use infliximab.
Infliximab can be transferred across the placenta. The baby is exposed to infliximab in the uterus of woman receiving infliximab during gestation and infliximab has been detected up to 12 months following birth. So, for these babies, there is an increased risk of infection, including fatal dispersivity infection. At least a 12 month waiting period following birth is recommended before the administration of any live vaccine to infants exposed in utero to infliximab.Lactation woman
Published literature show that infliximab is present at low levels in human milk. Systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract. Mother should stop breast feeding at least until 6 months after infliximab treatment.

Fecundity
There is no enough data to conduct a conclusion for relativity of infliximab and fecundity/ reproductive system function.

Pediatric use
Infliximab have been established for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active CD. Please remark in the phase III clinical trial (REACH), all patients should be combined with a stable dosage of 6-mercaptopurine, MTX or azathioprine.
However, the safety and effectiveness of INFLIXIMAB in pediatric patients <6 years of age with CD or UC or other diseases have not been established.
The PK of INFLIXIMAB have been established in 21 pediatric patients 6 to 17 years of age with CD.

After administration at dosage 5mg/kg, the PK character (including peak and trough concentration and terminal half-life) of infliximab in pediatric patients (6 to 17 years of age) and adult patients is similar.

Geriatric use

The specific study for geriatric patient has not been conducted.
In the INFLIXIMAB-treated patients in RA and Ps (181 RA patients and 75 Ps patients) clinical studies, no overall differences in safety or effectiveness were observed between geriatric patients (patients ≥65 years old) and younger adult patients (patients 18 to 65 years old). However, the incidence of serious adverse reactions in geriatric patients was higher in both INFLIXIMAB and control groups compared to younger adult patients.
In the INFLIXIMAB-treated patients in CD, UC, AS, and PsA clinical studies, there were insufficient numbers of geriatric patients to determine whether they respond differently from younger adults.
The incidence of serious infections in INFLIXIMAB-treated geriatric patients was greater than in INFLIXIMAB-treated younger adult patients; therefore close monitoring of geriatric patients for the development of serious infections is recommended

Drug interaction

Administration with anakinra or abatacept
Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra abatacept, with no added clinical benefit. Because of the nature of the adverse reactions seen with the concurrent use of TNF blockers therapy, similar toxicities may also result from the concurrent use of anakinra and abatacept. Therefore, the concurrent use of INFLIXIMAB and anakinra or abatacept is not recommended.

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

Administration with other biological products
The concurrent use of INFLIXIMAB with these biological products which have the same indication with infliximab is not recommended.

Administration with methotrexate or other medications
Specific drug interaction studies, including interactions with methotrexate (MTX), have not been conducted. The majority of patients in RA or CD clinical studies received one or more concomitant medications. In RA, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents (NSAIDs), folic acid, corticosteroids and/or narcotics. Concomitant CD medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates. In PsA clinical trials, concomitant medications included MTX in approximately half of the patients as well as NSAIDs, folic acid and corticosteroids. Concomitant MTX use may decrease the incidence of anti-infliximab antibody production and increase infliximab concentrations.

Immunosuppressants
Patients with CD who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants. Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of CD including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates.

Cytochrome P450 Substrates
The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-1, IL-6, IL-10, IFN) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as infliximab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of INFLIXIMAB in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

Live Vaccines/Therapeutic Infectious Agents
It is recommended that live vaccines and therapeutic infectious agents 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 at least 12 months following birth, unless infliximab is not detected or the benefit of vaccination (such as BCG, rotavirus vaccine, oral polio attenuated live vaccine, live attenuated measles and rubella vaccine, japanese encephalitis vaccine) obviously more than risk.. It is recommended to evaluate the risk and benefit of infant receiving vaccination during the treatment of gestation period.

Overdosage

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

Clinical studies

RA
The safety and efficacy of INFLIXIMAB in adult patients with RA were assessed in 2 multicenter, randomized, double-blind, pivotal trials: ATTRACT (anti-TNF study with concurrent use to treat RA) and ASPIRE (anti-RA study in early stage with infliximab treatment and active control). Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or non-steroidal anti-inflammatory drugs (NSAIDs) was permitted. The primary endpoint is to evaluate the decrease of signs and symptoms, prevention of joint injury and improvement of physical function based on specification of American College of Rheumatology (ACR).
ATTRACT was a placebo-controlled study of 428 patients with active RA despite treatment with MTX and evaluate the efficacy at 30th, 54th and 102th week. Patients enrolled had a median age of 54 years, median disease duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively and the physical function of about half of patients was class III. Patients received either placebo+MTX or one of 4 doses/schedules of INFLIXIMAB+MTX: 3 mg/kg or 10 mg/kg of INFLIXIMAB by IV infusion at Weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX.
ASPIRE was a placebo-controlled study of 3 active treatment arms in 1004 MTX naive patients of 3 or fewer years' duration active RA. Patients enrolled had a median age of 51 years with a median disease duration of 0.6 years, median swollen and tender joint count of 19 and 31, respectively. At randomization, all patients received MTX (optimized 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.
Data on use of INFLIXIMAB without concurrent MTX are limited. In above studies, the time of first three infusion were more than 2h. If no severe infusion reaction occur, the infusion time can be shortened but NLT 40min.
Clinical response

The decrease of signs and symptoms is defined as an at least 20% improvement (ACR20) in the three or more aspects of arthralgia and following 5 specification. The 5 specifications are healthcare provider evaluation, patients' self-evaluation, function/ disability evaluation, visual analogue pain scale and erythrocyte sedimentation rate (ESR) or c-reaction protein (CRP).
In Study ATTRACT, all doses/schedules of INFLIXIMAB+MTX resulted in improvement in signs and symptoms at 54th week as measured by the American College of Rheumatology response criteria (ACR 20) (Figure 1). This improvement was maintained through Week 102. Greater effects on each component of the ACR 50 and ACR 70 were observed in all patients treated with INFLIXIMAB+MTX compared to placebo+MTX (Table 3). The percent of patients with obvious efficacy (defined as maintain ACR 70 for 6 months) is 10% in INFLIXIMAB+MTX group, but in placebo+MTX group is 0% (p<0.018).

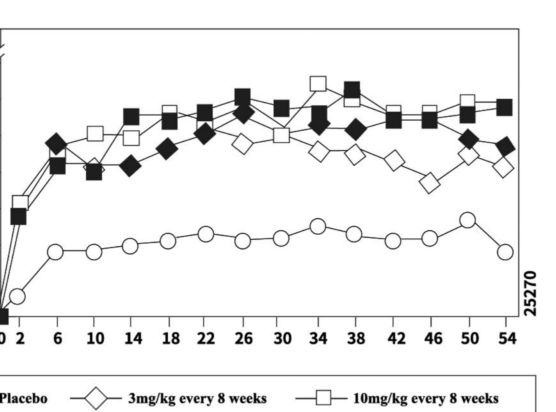

Figure 1: percentage of patients achieving ACR

Table 3: ACR in ATTRACT studies

Efficacy	Placebo + MTX	Infliximab + MTX			
		3mg/kg*every 8 weeks	3mg/kg*every 4 weeks	10mg/kg*every 8 weeks	10mg/kg*every 4 weeks
	N=88	N=86	N=86	N=87	N=81
ACR 50					
30th week	5%	27%	29%	31%	26%
54th week	5%	21%	34%	40%	38%
102th week	6%	21%	30%	36%	20%
ACR 70					
30th week	0%	8%	11%	18%	11%
54th week	2%	11%	18%	26%	19%
102th week	1%	10%	21%	20%	10%
Remark: p<0.05 compared to placebo group					

In Study ASPIRE, after 54 weeks of treatment, both doses of INFLIXIMAB+MTX resulted in statistically significantly greater response in signs and symptoms compared to MTX alone as measured by the proportion of patients achieving ACR 20, 50 and 70 responses (Table 4). The percent of patients with obvious efficacy is 15% in INFLIXIMAB group, but in MTX group is 8% (p=0.003).

Table 4: ACR in ASPIRE studies

Efficacy	MTX	Infliximab + MTX	
		3mg/kg*every 8 weeks	6mg/kg*every 8 weeks
	N=274	N=235	N=355
ACR 50			
54th week	54%	62%[3]	66%[b]
ACR 50			
54th week	32%	46%[b]	50%[b]
ACR 70			
54th week	21%	23%[c]	37%[b]
Remark a: p<0.05, b: p<0.01, c: p=0.02			

Radiographic response
Structural damage in both hands and feet was assessed radiographically at Week 54 by the change from baseline in the van der Heijde-modified Sharp (vdH-S) score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet.
In Study ATTRACT, approximately 80% of patients had paired X-ray data (Table 5). The inhibition of progression of structural damage was observed at 54 weeks and maintained through 102 weeks.

Table 5: Radiographic response in ATTRACT studies at Week 54

Median (10% and 90%)	Placebo + MTX	Infliximab + MTX				P value
		3mg/kg*every 8 weeks	3mg/kg*every 4 weeks	10mg/kg*every 8 weeks	10mg/kg*every 4 weeks	
Week 54	N=64	N=71	N=71	N=77	N=66	
Total Score						
Baseline	55(14,188)	57(15,187)	45(8,162)	56(6,143)	43(7,178)	
Change from baseline	4.0(-10,19.0)	0.5(-3.0,5.5)	0.1(-5.2,9.0)	0.5(-4.8,5.0)	-0.5(-5.7,4.0)	P<0.001
Erosion Score						
Baseline	25(8,110)	29(4,80)	22(3,91)	26(4,104)	26(4,104)	
Change from baseline	2.0(-10,9.7)	0.0(-3.0,4.3)	-0.3(-3.1,2.5)	-0.5(-2.7,2.5)	-0.5(-2.7,2.5)	P<0.001
JSN Score						
Baseline	26(3,88)	29(4,80)	20(3,83)	25(3,77)	25(3,77)	
Change from baseline	1.5(-0.8,8.0)	0.0(-2.5,4.5)	0.0(-3.4,5.0)	0.0(-3.0,3.5)	0.0(-3.0,3.5)	P<0.001

In Study ASPIRE, >90% of patients had at least 2 evaluable X-rays. Inhibition of progression of structural damage was observed at Weeks 30 and 54 (Table 6) in the INFLIXIMAB+MTX groups (97%) compared to MTX alone (86%). Patients treated with INFLIXIMAB+MTX demonstrated less progression of structural damage (79%) compared to MTX alone (57%) (Table 7). Patients treated with INFLIXIMAB+MTX demonstrated less new structural damage (47%) compared to MTX alone (59%) (Table 8).

Table 6: Radiographic response in ASPIRE studies at Week 54

Median (10% and 90%)		Infliximab + MTX			P value
	MTX	3mg/kg*every 8 weeks	6mg/kg*every 8 weeks		
Week 54	N=279	N=355	N=360		
Total Score					
Baseline	5.5 (1.40, 14.50)	5.25 (1.75, 15.5)	5.25 (1.75, 14.20)		
Change from baseline	0.43 (0.00, 4.53)	0.00 (-0.75, 1.25)	0.43 (-1.00, 1.25)		P<0.001
Erosion Score					
Baseline	3.00 (0.50, 10.50)	3.75 (1.00, 11.00)	3.75 (1.00, 10.75)		
Change from baseline	0.25 (0.00, 3.75)	0.00 (-0.75, 1.25)	0.00 (0.00, 0.20)		P<0.001
JSN Score					
Baseline	1.00 (0.00, 3.90)	1.00 (0.00, 3.80)	1.00 (0.00, 3.80)		
Change from baseline	0.00 (0.00, 0.40)	0.00 (0.00, 0.00)	0.00 (0.00, 0.20)		P<0.001

Table 7: No joint erosion in ASPIRE studies at Week 54

	MTX	Infliximab + MTX		Total
		3mg/kg*every 8 weeks	6mg/kg*every 8 weeks	
	N=282	N=359	N=363	N=772
Patients with 0 erosion baseline score	227	50	48	98
Patients with 0 erosion score at week 54	23 (57%)	39(78%)	38(79%)	77(79%)
P value		0.037	0.038	0.012

Table 8: New joint erosion in ASPIRE studies at Week 54

	MTX	Infliximab + MTX		Total
		3mg/kg*every 8 weeks	6mg/kg*every 8 weeks	
	N=282	N=359	N=363	N=772
Patients with previous erosion score NLT 1	227	306	306	712
Patients without new joint erosion at week 54	93(41%)	155(51%)	168(55%)	323(53%)
P value		0.027	0.001	0.002

Physical function response
In Study ATTRACT, all doses/schedules of INFLIXIMAB+MTX showed significantly greater improvement compared to placebo+MTX at week 102. Life quality related to health were assessed using the general health-related quality of life questionnaire SF-36. The 8 sub-evaluation were combined in two overall scores (physical score and mental score). After 102 weeks, all doses/schedules of INFLIXIMAB+MTX showed significantly greater improvement in physical function and no adverse effect in mental aspect compared to placebo+MTX (Table 9).

Table 9: Physical function improvement in ATTRACT studies at Week 102

	Placebo + MTX	Infliximab + MTX				P value
		3mg/kg*every 8 weeks	3mg/kg*every 4 weeks	10mg/kg*every 8 weeks	10mg/kg*every 4 weeks	
HAQ-DI						
Number of patients	88	86	85	87	81	
Median	0.1	0.4	0.4	0.4	0.3	P<0.006
Inter-quartile range	(0.0, 0.4)	(0.1, 0.6)	(0.1, 0.7)	(0.2, 0.9)	(0.1, 0.5)	
SF-36 Score						
Number of patients	88	84	86	86	79	
Median	2.8	4.6	6.8	6.9	6.7	P<0.011
Inter-quartile range	(0.5, 5.8)	(1.3, 9.5)	(3.1, 15.7)	(1.8, 14.8)	(2.8, 11.4)	

In Study ASPIRE, both INFLIXIMAB treatment groups showed greater improvement in the physical function of the Health Assessment Questionnaire (HAQ-DI) compared to MTX alone (Table 10); 0.7 for INFLIXIMAB+MTX vs. 0.6 for MTX alone (P≤0.001). No worsening in the SF-36 mental component summary score was observed.

Table 10: Physical function improvement in ASPIRE studies at Week 54

	MTX	Infliximab + MTX	
		3mg/kg*every 8 weeks	6mg/kg*every 8 weeks
HAQ-DI			
Number of patients	275	354	358
Median	0.57	0.64	0.76
Inter-quartile range	(0.16, 0.90)	(0.29, 1.07)	(0.28, 1.20)
P value		<0.001	
SF-36 Score			
Number of patients	226	303	302
Median	8.9	10.9	11.8
Inter-quartile range	(1.4, 18.9)	(2.6, 19.8)	(4.4, 21.2)
P value		0.099	0.003
The data for infliximab not combined with MTX is limited.			

Active crohn's disease
The safety and efficacy of single and multiple doses of INFLIXIMAB were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 653 adult patients with moderate to severely active CD (Crohn's Disease Activity Index (CDAI) ≥220 and ≤400) with an inadequate response to prior conventional therapies. Concomitant stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted and 92% of patients continued to receive at least one of these medications.
In the single-dose trial of 108 adult patients, 16% (4/25) of placebo patients achieved a clinical response (decrease in CDAI ≥70 points) at Week 4 vs. 81% (22/27) of patients receiving 5 mg/kg INFLIXIMAB (p<0.001, two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo patients and 48% (13/27) of patients receiving 5 mg/kg INFLIXIMAB achieved clinical remission (CDAI<150) at Week 4.
In a multi-dose trial (ACCENT I [Study Crohn's I]), 545 adult patients received 5 mg/kg at Week 0 and were then randomized to one of three treatment groups; the placebo maintenance group received placebo at Weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in response at Week 2 were randomized and analyzed separately from those not in response at Week 2. Corticosteroid taper was permitted after Week 6.
At Week 2, 57% (311/545) of patients were in clinical response. At Week 30, a significantly greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved clinical remission compared to patients in the placebo maintenance group (Table 11).
Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg INFLIXIMAB maintenance groups were in clinical remission and were able to discontinue corticosteroid use compared to patients in the placebo maintenance group at Week 54 (Table 11).

Table 11: Clinical Remission and Steroid Withdrawal in Adult Patients with CD (Study Crohn's I)

	Single 5-mg/kg Dose[a]	Three-Dose Induction[b]	
	Placebo Maintenance	INFLIXIMAB Maintenance every 8 weeks	
		5 mg/kg	10 mg/kg
Week 30	25/102	41/104	48/105
Clinical remission	25%	39%	46%
P-value[c]		0.022	0.001
Week 54	6/54	14/56	18/53
Patients in remission able to discontinue corticosteroid use[d]	11%	25%	34%
P-value[c]		0.059	0.005

Remark a: INFLIXIMAB at Week 0
Remark b: INFLIXIMAB 5 mg/kg administered at Weeks 0, 2 and 6
Remark c: P-values represent pairwise comparisons to placebo
Remark d: Of those receiving corticosteroids at baseline

Patients in the INFLIXIMAB maintenance groups (5 mg/kg and 10 mg/kg) had a longer time to loss of response than patients in the placebo maintenance group (Figure 2).
At Weeks 30 and 54, significant improvement from baseline was seen among the 5 mg/kg and 10 mg/kg INFLIXIMAB-treated groups compared to the placebo group in the disease-specific inflammatory bowel disease questionnaire (IBDQ), particularly the bowel and systemic components, and in the physical component summary score of the general health-related quality of life questionnaire SF-36.

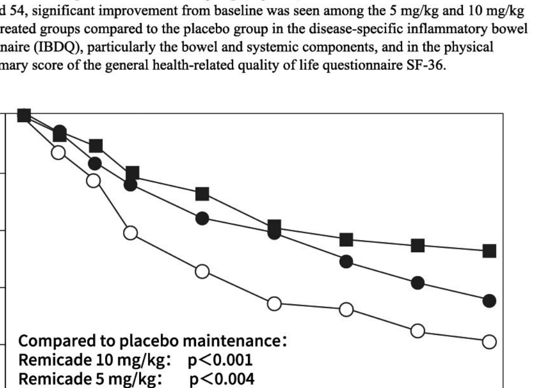

Figure 2:Kaplan-Meier Estimate of the Proportion of Adults with CD Who Had Not Lost Response Through Week 54 (Study Crohn's I)

In a subset of 78 patients who had mucosal ulceration at baseline and who participated in an endoscopic substudy, 13 of 43 patients in the INFLIXIMAB maintenance group had endoscopic evidence of mucosal healing compared to 1 of 28 patients in the placebo group at Week 10. Of the INFLIXIMAB-treated patients showing mucosal healing at Week 10, 9 of 12 patients also showed mucosal healing at Week 54. 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 randomized. The majority of such patients responded to the higher dose. Among patients who were not in response at Week 2, 59% (92/157) of INFLIXIMAB maintenance patients responded by Week 14 compared to 51% (39/77) of placebo maintenance patients. Among patients who did not respond by Week 14, additional therapy did not result in significantly more responses

Fistulizing Crohn's Disease
The safety and efficacy of INFLIXIMAB were assessed in 2 randomized, double-blind, placebo-controlled studies in adult patients with fistulizing CD with fistula(s) that were of at least 3 months duration. Concurrent use of stable doses of corticosteroids, 5-aminosalicylates, antibiotics, MTX, 6-mercaptopurine (6-MP) and/or azathioprine (AZA) was permitted.
In the first trial, 94 adult patients received 3 doses of either placebo or INFLIXIMAB at Weeks 0, 2 and 6. Fistula response (≥50% reduction in number of enterocutaneous fistulas draining upon gentle compression on at least 2 consecutive visits without an increase in medication or surgery for CD) was seen in 68% (21/31) of patients in the 5 mg/kg INFLIXIMAB group (P=0.002) and 56% (18/32) of patients in the 10 mg/kg INFLIXIMAB group (P=0.021) vs. 26% (8/31) of patients in the placebo arm. The median time to onset of response and median duration of response in INFLIXIMAB-treated patients was 2 and 12 weeks, respectively. Closure of all fistulas was achieved in 52% of INFLIXIMAB-treated patients compared with 13% of placebo- treated patients (P<0.001).
In the second trial (ACCENT II [Study Crohn's II]), adult patients who were enrolled had to have at least 1 draining enterocutaneous (perianal, abdominal) fistula. All patients received 5 mg/kg INFLIXIMAB at Weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg INFLIXIMAB maintenance at Week 14. Patients received maintenance doses at Week 14 and then every 8 weeks through Week 46. Patients who were in fistula response (fistula response was defined the same as in the first trial) at both Weeks 10 and 14 were randomized separately from those not in response. The primary endpoint was time from randomization to loss of response among those patients who were in fistula response.
Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of the patients had received previous immunosuppressive and antibiotic therapy.
At Week 14, 65% (177/273) of patients were in fistula response. Patients randomized to INFLIXIMAB maintenance had a longer time to loss of fistula response compared to the placebo maintenance group (Figure 3). 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). Compared to placebo maintenance, patients on INFLIXIMAB maintenance had a trend toward fewer hospitalizations.

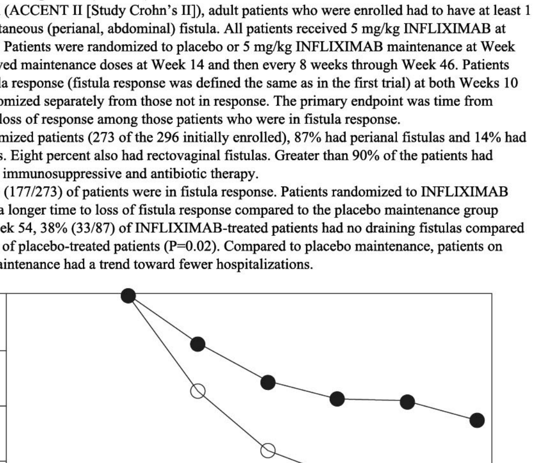

Figure 3:Life Table Estimates of the Proportion of Adult CD Patients Who Had Not Lost Fistula Response Through Week 54 (Study Crohn's II)

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 randomized. 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.
Patients who had not achieved a response by Week 14 were unlikely to respond to additional doses of INFLIXIMAB.
Similar proportions of patients in either group developed new fistulas (17% overall) and similar numbers developed abscesses (15% overall).

Pediatric Crohn's Disease
The safety and efficacy of INFLIXIMAB were assessed in a randomized, open-label study (REACH study) in 112 pediatric patients aged 6 to 17 years old (the median Pediatric Crohn's Disease Activity Index (PCDAI) was 40) with moderately to severely active CD and an inadequate response to conventional therapies. All patients were required to be on a stable dose of 6-MP, AZA, or MTX; 35% were also receiving corticosteroids at baseline.
All patients received induction dosing of 5 mg/kg INFLIXIMAB at Weeks 0, 2, and 6. At Week 10, patients with clinical response (88.4%, 99/112) were randomized to a maintenance regimen of 5 mg/kg INFLIXIMAB given either every 8 weeks or every 12 weeks. The other patients without clinical response were permitted to transfer to a higher dosage (10mg/kg) or shorten the administration interval (8 weeks). At Week 10, percent of patients with clinical remission were 58.9% (66/112). At week 30, percent of the clinical remission in the every 8-week treatment group is higher (59.6%, 31/52) than in the every 12-week treatment group (35.3%, 18/51; p=0.013). At week 54, percent of the clinical remission in the every 8-week treatment group is higher (55.8%, 29/52) than in the every 12-week treatment group (23.5%, 12/51; p<0.001).
For patients receiving corticosteroids at baseline, the proportion of patients able to discontinue corticosteroids while in remission at Week 30 was 45.8% for the every 8-week maintenance group and 33.3% for the every 12-week maintenance group. At Week 54, the proportion of patients able to discontinue corticosteroids while in remission was 45.8% for the every 8-week maintenance group and 16.7% for the every 12-week maintenance group.

Ankylosing spondylitis
The safety and efficacy of INFLIXIMAB were assessed in a randomized, multicenter, double- blind, placebo-controlled study in 279 adult patients with active AS. Patients were between 18 and 74 years of age, and had AS, as defined by the modified New York criteria for Ankylosing Spondylitis. Patients were to have had active disease as evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4 (possible range 0-10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10). Patients with complete ankylosis of the spine were excluded from study participation, and the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were prohibited. Doses of INFLIXIMAB 5mg/kg or placebo were administered intravenously at Weeks 0, 2, 6, 12 and 18. At 24 weeks, improvement in the signs and symptoms of AS, as measured by the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20), was seen in 60% of patients in the INFLIXIMAB-treated group vs. 18% of patients in the placebo group (p<0.001). Improvement was observed at Week 2 and maintained through Week 24 (Figure 4 and Table 12).

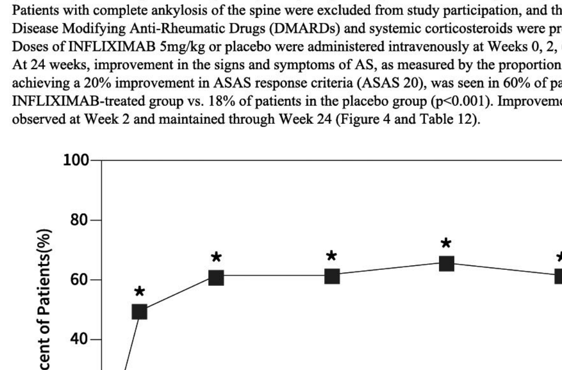

Figure 4:Proportion of Adult AS Patients Who Achieved an ASAS 20 Response

At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs and symptoms of AS, as measured by ASAS response criteria (ASAS 50 and ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving INFLIXIMAB, compared to 9% and 4%, respectively, for patients receiving placebo (P<0.001, INFLIXIMAB vs. placebo). A low level of disease activity (defined as a value <20 [on a scale of 0-100 mm] in each of the 4 ASAS response parameters) was achieved in 22% of INFLIXIMAB-treated patients vs. 1% in placebo-treated patients (P<0.001).

Table 12: Components of AS Disease Activity

	Placebo (n=78)		INFLIXIMAB 5 mg/kg (n=201)		P-value
	Baseline	24 Weeks	Baseline	24 Weeks	
ASAS 20 response					
Criteria (Mean)					
Patient Global Assessment[a]	6.6	6.0	6.8	3.8	<0.001
Spinal pain[a]	7.3	6.5	7.6	4.0	<0.001
BASFI[b]	5.8	5.6	5.7	3.6	<0.001
Inflammation[c]	6.9	5.8	6.9	3.4	<0.001
Acute Phase Reactants					
Median CRP[d] (mg/dL)	1.7	1.5	1.5	0.4	<0.001
Spinal Mobility (cm, Mean)					
Modified Schober's test[e]	4.0	5.0	4.3	4.4	0.75
Chest expansion[e]	3.6	3.7	3.3	3.9	0.04
Tragus to wall[e]	17.3	17.4	16.9	15.7	0.02
Lateral spinal flexion[e]	10.6	11.0	11.4	12.9	0.03

Remark a: Measured on a VAS with 0="none" and 10="severe"
Remark b: Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions
Remark c: Inflammation, average of last 2 questions on the 6-question BASDAI
Remark d: CRP normal range 0-1.0 mg/dL
Remark e: Spinal mobility normal values: modified Schober's test: >4 cm; chest expansion: >6 cm; tragus to wall: <15 cm; lateral spinal flexion: >10 cm
The median improvement from baseline in the general health-related quality-of-life questionnaire SF-36 physical component summary score at Week 24 was 10.2 for the INFLIXIMAB group vs. 0.8 for the placebo group (P<0.001). There was no change in the SF 36 mental component summary score in either the INFLIXIMAB group or the placebo group.
Results of this study were similar to those seen in a multicenter double-blind, placebo- controlled study of 70 patients with AS.

Plaque psoriasis
The safety and efficacy of INFLIXIMAB were assessed in 3 randomized, double-blind, placebo-controlled studies in patients 18 years of age and older with chronic, stable Ps involving ≥10% BSA, a minimum PASI score of 12, and who were candidates for systemic therapy or phototherapy. Patients with guttate, pustular, or erythrodermic psoriasis were excluded from these studies. No concomitant anti-psoriatic therapies were allowed during the study, with the exception of low-potency topical corticosteroids on the face and groin after Week 10 of study initiation.
Study I (EXPRESS) evaluated 378 patients who received placebo or INFLIXIMAB at a dose of 5 mg/kg at Weeks 0, 2, and 6 (induction therapy), followed by maintenance therapy every 8 weeks. At Week 24, the placebo group crossed over to INFLIXIMAB induction therapy (5 mg/kg), followed by maintenance therapy every 8 weeks. Patients originally randomized to INFLIXIMAB continued to receive INFLIXIMAB 5 mg/kg every 8 weeks through Week 46. Across all treatment groups, the median baseline PASI score was 21 and the baseline Static Physician Global Assessment (sPGA) score ranged from moderate (52% of patients) to marked (36%) to severe (2%). In addition, 75% of patients had a BSA >20%. Seventy-one percent of patients previously received systemic therapy, and 82% received phototherapy.
Study II (EXPRESS II) evaluated 835 patients who received placebo or INFLIXIMAB at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6 (induction therapy). At Week 14, within each INFLIXIMAB dose group, patients were randomized to either scheduled (every 8 weeks) or as needed (PRN) maintenance treatment through Week 46. At Week 16, the placebo group crossed over to INFLIXIMAB induction therapy (5 mg/kg), followed by maintenance therapy every 8 weeks. Across all treatment groups, the median baseline PASI score was 18, and 63% of patients had a BSA >20%. Fifty-five percent of patients previously received systemic therapy, and 64% received a phototherapy.
Study III (SPIRIT) evaluated 249 patients who had previously received either psoralen plus ultraviolet A treatment (PUVA) or other systemic therapy for their psoriasis. These patients were randomized to receive either placebo or INFLIXIMAB at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6. At Week 26, patients with a sPGA score of moderate or worse (greater than or equal to 3 on a scale of 0 to 5) received an additional dose of the randomized treatment. Across all treatment groups, the median baseline PASI score was 19, and the baseline sPGA score ranged from moderate (62% of patients) to marked (22%) to severe (3%). In addition, 75% of patients had a BSA >20%. Of the enrolled patients, 114 (46%) received the Week 26 additional dose.
In Studies I, II and III, the primary endpoint was the proportion of patients who achieved a reduction in score of at least 75% from baseline at Week 10 by the PASI (PASI 75). In Study I and Study III, another evaluated outcome included the proportion of patients who achieved a score of "cleared" or "minimal" by the sPGA. The sPGA is a 6-category scale ranging from "5 = severe" to "0 = cleared" indicating the physician's overall assessment of the psoriasis severity focusing on induration, erythema, and scaling. Treatment success, defined as "cleared" or "minimal," consisted of none or minimal elevation in plaque, up to faint red coloration in erythema, and none or minimal fine scale over <5% of the plaque.
Study II also evaluated the proportion of patients who achieved a score of "clear" or "excellent" by the relative Physician's Global Assessment (rPGA). The rPGA is a 6-category scale ranging from "6 = worse" to "1 = clear" that was assessed relative to baseline. Overall lesions were graded with consideration to the percent of body involvement as well as overall induration, scaling, and erythema. Treatment success, defined as "clear" or "excellent," consisted of some residual pinkness or pigmentation to marked improvement (nearly normal skin texture; some erythema may be present). The results of these studies are presented in Table 13.

Table 13: Adult Psoriasis Studies I, II, and III, Percentage of Patients who Achieved PASI 75 and Percentage who Achieved Treatment "Success" with Physician's Global Assessment at Week 10

	Placebo	INFLIXIMAB	
		3 mg/kg	5 mg/kg
Psoriasis Study I - patients randomized[a]	77	—	301
PASI 75	2 (3%)	—	242 (80%)*
sPGA	3 (4%)	—	242 (80%)*
Psoriasis Study II - patients randomized[a]	208	313	314
PASI 75	4 (2%)	220 (70%)*	237 (75%)*
rPGA	2 (1%)	217 (69%)*	234 (75%)*
Psoriasis Study III - patients randomized[a]	51	99	99
PASI 75	3 (6%)	71 (72%)*	87 (88%)*
sPGA	5 (10%)	71 (72%)*	89 (90%)*

Remark *: P<0.001 compared with placebo
Remark a: Patients with missing data at Week 10 were considered as nonresponders.
Remark b: Patients with missing data at Week 10 were imputed by last observation.
In Study I, in the subgroup of patients with more extensive Ps who had previously received phototherapy, 85% of patients on 5 mg/kg INFLIXIMAB achieved a PASI 75 at Week 10 compared with 4% of patients on placebo.
In Study II, in the subgroup of patients with more extensive Ps who had previously received phototherapy, 72% and 77% of patients on 3 mg/kg and 5 mg/kg INFLIXIMAB achieved a PASI 75 at Week 10 respectively compared with 1% on placebo. In Study II, among patients with more extensive Ps who had failed or were intolerant to phototherapy, 70% and 78% of patients on 3 mg/kg and 5 mg/kg INFLIXIMAB achieved a PASI 75 at Week 10 respectively, compared with 2% on placebo.
Maintenance of response was studied in a subset of 292 and 297 INFLIXIMAB-treated patients in the 3 mg/kg and 5 mg/kg groups; respectively, in Study II. Stratified by PASI response at Week 10 and investigational site, patients in the active treatment groups were re-randomized to either a scheduled or as needed maintenance (PRN) therapy, beginning on Week 14.
The groups that received a maintenance dose every 8 weeks appear to have a greater percentage of patients maintaining a PASI 75 through Week 50 as compared to patients who received the as-needed or PRN doses, and the best response was maintained with the 5 mg/kg every 8-week dose. These results are shown in Figure 5. At Week 46, when INFLIXIMAB serum concentrations were at trough level, in the every 8-week dose group, 54% of patients in the 5 mg/kg group compared to 36% in the 3 mg/kg group achieved PASI 75. The lower percentage of PASI 75 responders in the 3 mg/kg every 8-week dose group compared to the 5 mg/kg group was associated with a lower percentage of patients with detectable trough serum infliximab levels. This may be related in part to higher antibody rates [see Adverse Reactions (6.1)]. In addition, in a subset of patients who had achieved a response at Week 10, maintenance of response appears to be greater in patients who received INFLIXIMAB every 8 weeks at the 5 mg/kg dose. Regardless of whether the maintenance doses are PRN or every 8 weeks, there is a decline in response in a subpopulation of patients in each group over time. The results of Study I through Week 50 in the 5 mg/kg every 8 weeks maintenance dose group were similar to the results from Study II.

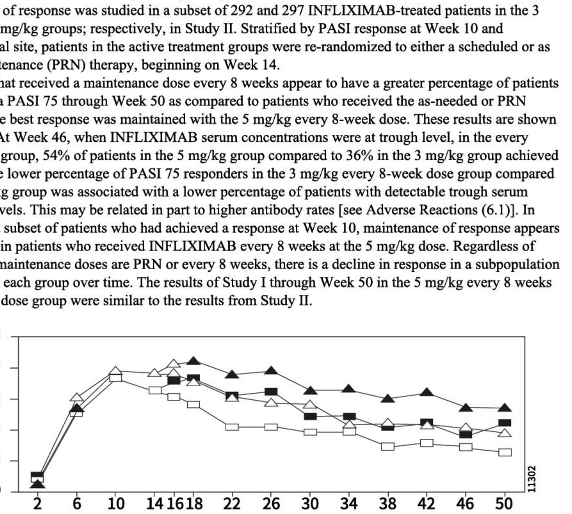

Figure 5:Proportion of Adult Ps Patients Who Achieved ≥75% Improvement in PASI from Baseline through Week 50 (patients randomized at Week 14)

Efficacy and safety of INFLIXIMAB treatment beyond 50 weeks have not been evaluated in patients with Ps.

Ulcerative colitis
The safety and efficacy of INFLIXIMAB were assessed in 2 randomized, double-blind, placebo-controlled clinical studies (ACT 1 and ACT 2) in adult patients with moderately to severely active UC (Mayo score 6 to 12 [of possible range 0 to 12], Endoscopy subscore ≥2) with an inadequate response to conventional oral therapies (aminosalicylates, corticosteroids and/or immunomodulatory agents 6-MP, AZA). Concomitant treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents was permitted. Patients were randomized at week 0 to receive either placebo, 5 mg/kg INFLIXIMAB or 10 mg/kg INFLIXIMAB at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 46 in ACT 1, and at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 22 in ACT 2.Corticosteroid taper was permitted after Week 8.

Table 14: Response, Remission and Mucosal Healing in Adult UC Studies (ACT 1 and ACT 2)

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Total
Patients randomized	244	242	242	484
Clinical response and continuous clinical response				
Week 8	33.2%	66.9%*	65.3%*	66.1%
Week 30	27.9%	49.6%%	55.4%%	52.5%
Continuous response both in week 8 and 30	19.3%	45.0%*	49.6%*	47.3%
Clinical remission and continuous remission				
Week 8	10.2%	36.4%	29.8%	33.1%
Week 30	13.1%	29.8%*	36.4%*	33.1%
Continuous remission both in week 8 and 30	5.3%	19.0%	24.4%	21.7%
Mucosal Healing				
Week 8	32.4%	61.2%*	60.3%	60.7%
Week 30	27.5%	48.3%*	52.9%*	50.6%

Remark: for each infliximab group, the P id <0.001 compared to placebo group.
In ACT 1 study, the efficacy of infliximab was evaluated at week 54. At week 54, 44.9% patients in infliximab group received clinical response, but in placebo group was 19.8% (p<0.001). At week 54, the percent of patients receiving clinical remission and mucosal healing in infliximab group was higher than placebo group (34.6% vs 16.5%, p<0.001 and 46.1% vs 18.2%, p<0.001) in both ACT 1 and ACT 2 study. At week 54, the percent of patients receiving continuous clinical response and continuous clinical remission in infliximab group was higher than placebo group (37.9% vs 14.0%, p<0.001 and 20.2% vs 6.6%, p<0.001) in both ACT 1 and ACT 2 study.
At week 30 and week 54, the percent of patients maintaining clinical remission after corticosteroids withdraw in infliximab group was higher than placebo group (22.3% vs 7.2%, p<0.001) in both ACT 1 and ACT 2 study.
From baseline to week 54, all data from ACT 1, ACT 2 study and extended period indicated that the hospitalization and surgery related to UC decreased after treatment with infliximab. Hospitalization times related to UC in 5mg/kg and 10mg/kg infliximab group was much lower than placebo group (average times/100 patients/year: 21 and 19 vs 40 in placebo group, p=0.019 and 0.007 respectively). Surgery times related to UC in 5mg/kg and 10mg/kg infliximab group was also lower than placebo group (average times/100 patients/year: 22 and 19 vs 34 in placebo group, p=0.145 and 0.022 respectively).
From baseline to week 54, all patients undergoing colectomy at any time in ACT 1, ACT 2 study and extended period were calculated the percent (28/242 or 11.6%, no obvious difference in 5mg/kg infliximab group and 18/242 or 7.4%, p=0.011 in 10mg/kg infliximab group) . The percent was much less than placebo group (36/244, 14.8%).
The efficacy of INFLIXIMAB in decrease of incidence of colectomy were assessed in another randomized, double-blind, clinical studies (C0168Y06) in patients (n=45) with moderately to severely active UC and a high risk in colectomy with an inadequate response to corticosteroids therapies. In 5mg/kg single dose infliximab group, the percent of patients undergoing colectomy within 3 months after treatment was much lower than placebo group (29.2% and 66.7% respectively, p=0.017).
In both ACT 1 and ACT 2 study, disease-specific inflammatory bowel disease questionnaire (IBDQ) and general health-related quality of life questionnaire (SF-36) both indicated that there is statistically significant improvement and it proved infliximab can improve the life quality.

Clinical pharmacology

Mechanism of action
Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors. Infliximab does not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes.

Nonclinical toxicity

Genetic toxicity
The result of Ames study, human lymphocyte chromosomal aberration study and mice micronucleus study were all negative.

Reproduction toxicity
There is no cross-reactivity for infliximab with TNFα in other species except for human and chimpanzee so that reproduction toxicity study is not conducted.
cV1q is a kind of an analogous antibody which is selective anti- mouse TNFα. No impairment of fertility or reproductive performance indices were observed in male or female mice that received cV1q, an analogous mouse antibody, at intravenous doses up to 40 mg/kg given weekly. At 6th and 12th day of gestation, no evidence of maternal toxicity, embryonic death or teratogenicity was observed in mice that received intravenous doses of 40 mg/kg cV1q. At 14th day of gestation, the analysis of embryo indicated that antibody can pass through the placenta and make embryo exposed in antibody during organ development period. In mice perinatal toxicity study, No maternal toxicity or impairment of offspring were observed in mice that received cV1q, at intravenous doses 10mg/kg or 40mg/kg at 6th, 12th and 18th day of gestation and 3th, 9th and 15th day of lactation period.

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

Pharmacokinetics

In adults, single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg (two times the maximum recommended dose for any indication) showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg to 10 mg/kg in RA, 5 mg/kg in CD, and 3 mg/kg to 5 mg/kg in Ps indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days.
Following an initial dose of INFLIXIMAB, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8 weeks after a maintenance dose of 3 to 10 mg/kg of INFLIXIMAB, median infliximab serum concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.
Infliximab pharmacokinetic characteristics (including peak and trough concentrations and terminal half-life) were similar in pediatric (aged 6 to 17 years) and adult patients with CD or UC following the administration of 5 mg/kg of INFLIXIMAB.
The population pharmacokinetics analysis based on data from patients with UC (n=60), CD (n=112), RA (n=117) and kawasaki disease (n=16) (age from 2 month old to 17 years old) indicated that the total clearance rate of infliximab does not increase linearly with increase of weight. So for infliximab administrated in 5mg/kg dosage every 8 weeks, median stable exposure level for 6 to 17 years old children (area under stable concentration-time curve, AUCss) is estimated to be 20% lower than adult. The median AUCss in 2 to 6 years old children is estimated to be 40% lower than adult. Above estimation is based on the data from limited patients.

Storage

2-8°C, prevent from light.

Package

1 vial/box

Expired date

36 months

Specification

YBS00582021

BLA number

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MAH

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