INFLECTRA®

PRODUCT INFORMATION

NAME OF THE MEDICINE

INFLECTRA® infliximab (rmc) 100mg Powder for Injection

DESCRIPTION

Each vial of INFLECTRA® contains infliximab 100 mg. Infliximab is a chimeric human-murine IgG monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology. After reconstitution each ml contains 10 mg of infliximab. Inactive Ingredients: sodium phosphate monobasic monohydrate, sodium phosphate dibasic dihydrate, sucrose and polysorbate 80.

INFLECTRA® (infliximab) is an approved biosimilar to the reference product REMICADE® (infliximab). Comparability in safety, efficacy and quality between INFLECTRA® and REMICADE® has been established.

PHARMACOLOGY

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

Cellular responses to TNFα include:

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

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

Infliximab neutralises the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors. Infliximab does not neutralise TNFβ (lymphotoxin α), a related cytokine that utilises the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as IL-1 and IL-6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity and induction of acute phase and other liver proteins. Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro* by complement or effector cells. Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilising human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells.

Pharmacodynamics

Elevated concentrations of TNFα have been found in the sera and stools of adult Crohn's disease patients and in the joints of rheumatoid arthritis patients and correlate with elevated disease activity. Increased concentrations of TNFα have also been found in joint fluid/tissue and in psoriatic skin lesions in patients with psoriatic arthritis. In psoriatic arthritis, treatment with Infliximab resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin as well as a reduction of macrophages in the synovium. In patients with Crohn's disease, treatment with infliximab reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine; it

also reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon γ. In patients with rheumatoid arthritis, treatment with Infliximab reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion, chemoattraction and tissue degradation. After treatment with Infliximab, patients with rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to their baseline values. In patients with rheumatoid arthritis, peripheral blood lymphocytes further showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to untreated patients' cells. In psoriasis patients, treatment with infliximab resulted in decreases in epidermal inflammation and normalization of keratinocyte differentiation in psoriatic plaques.

Comparability of INFLECTRA® with REMICADE®

As part of the pharmaceutical and nonclinical development programme of INFLECTRA®, 33 *in vitro* tests in comparison to REMICADE® have been conducted. These tests covered investigations of the binding affinity of INFLECTRA® and REMICADE® for human TNFα, for soluble human TNFα in trimeric and monomeric forms, for tmTNFα-Jurkat cells, Fcγ receptors (FcγRI, FcγRIIa and FcγRIIIa), neonatal Fc receptor, and to C1q as well as tests on tissues cross reactivities. Overall, these tests found that INFLECTRA® and REMICADE® are comparable. In addition, functional tests showed that INFLECTRA® and REMICADE® are comparable with regard to neutralising TNFα, complement-dependent cytotoxicity (CDC), apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC). Both products did not show any binding affinity for TNFß.

Pharmacokinetics

In clinical trials in rheumatoid arthritis and Crohn's disease patients, single dose intravenous infusions of 1, 3, 5, 10 or 20 mg/kg of infliximab yielded dose proportional increases in the maximum serum concentration (Cmax) and area under the concentration-time curve (AUC). The volume of distribution at steady state (median Vss of 3.0 to 4.1 litres) was not dependent on the administered dose and indicated that infliximab is predominantly distributed within the vascular compartment. The elimination pathways for infliximab have not been characterised. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight or hepatic or renal function. Paediatric Crohn's patients in the 5 mg/kg and 10 mg/kg treatment groups had slightly higher serum concentrations after the initial infusion and slightly lower serum concentrations at later time periods (4 to 12 weeks) compared to adult Crohn's patients. No notable differences in single dose pharmacokinetic parameters and terminal half-life were observed between paediatric and adult Crohn's disease patients. The relatively small number of patients evaluated makes further detailed comparison difficult.

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

At single doses of 3 and 10 mg/kg in rheumatoid arthritis patients and 5 mg/kg in Crohn's disease patients, the median C_{max} values were 77 and 277 μg/mL and 118 μg/mL respectively. The median terminal half-life at these doses ranged from 8 to 9.5 days. In most patients, infliximab could be detected in the serum for at least 8 weeks after a single infusion. Following the 3-dose regimen a slight accumulation of infliximab was observed in the serum after the second dose and no further clinically relevant accumulation thereafter. The proportion of patients who had undetectable infliximab concentrations at 8 weeks, after a maintenance infusion, was approximately 20%.

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

Comparability of INFLECTRA® with REMICADE®

Equivalent pharmacokinetic (PK) profiles of INFLECTRA® and REMICADE® have been demonstrated in a randomised, double-blind, parallel-group, Phase 1 study in patients with ankylosing spondylitis (AS).

Mean values for AUC_{tau} and $C_{MAX,SS}$ were similar between the treatment groups and the 90% CIs of ratio of geometric means for both AUC_{tau} and $C_{max,ss}$ were entirely within the reference range of 80–125% indicating that INFLECTRA® is bioequivalent to the reference product REMICADE® in terms of AUC_{tau} and $C_{max,ss}$. The pharmacokinetic parameters are summarized in Table 1.

Table 1. Primary Serum Pharmacokinetic Parameters of the PK Population between Week 22 and 30 (Study PLANET AS in Ankylosing Spondylitis)

Parameter	INFLECTRA® (5 mg/kg) (n=112)	REMICADE® (Schering-Plough, Belgium) (5 mg/kg) (n=110)	Ratio (%) of Geometric Mean	90% CI of Ratio
AUC_{tau} (µg*h/mL)	32,750.99 (n=112)	31,366.00 (n=110)	104.42	94.25 – 115.67
$C_{MAX,SS}$ (µg/mL)	147.04 (n=113)	144.81 (n=110)	101.53	94.67 – 108.89
$C_{MIN,SS}$ (µg/mL)	4.23 (139.5) (n=108)	3.59 (88.1) (n=108)		
$T_{½}$ (h)	291.27 (32.3) (n=102)	298.31 (32.9) (n=98)		

AUCτ=Area under the concentration-time curve over the dosing interval; $C_{MAX,SS}$=Maximum serum concentration at steady state; $C_{MIN,SS}$=Minimum serum concentration at steady state; T_{MAX}=Time to reach C_{MAX}; CI=Confidence interval

The following secondary PK endpoints, C_{min}, C_{max} and T_{max} were assessed up to week 54 and these results remained comparable.

These results are supported by the PK evaluation in a Phase 3 randomised, double-blind, multicentre, parallel-group study in patients with active Rheumatoid Arthritis (RA). The analyses of the secondary PK parameters showed that the PK profile of INFLECTRA® is comparable to REMICADE® in this patient population as well. The pharmacokinetic parameters are summarized below in Table 2 and Table 3.

Table 2: Geometric mean (%CV) of Infliximab at Week 30 (PK population) - Study PLANET RA in Rheumatoid Arthritis

Parameter	INFLECTRA® (3 mg/kg) (n=292)	REMICADE® (Schering-Plough, Belgium) (3 mg/kg) (n=289)
C_{MAX} (µg/mL)	83.87 (38) (n=243)	83.78 (35) (n=245)
T_{MAX} (h)	2.08 (2.00, 3.58) (n=243)	2.25 (0.10, 3.33) (n=245)

$C_{MAX,SS}$=Maximum serum concentration at steady state; $C_{MIN,SS}$=Minimum serum concentration at steady state; T_{MAX}=Time to reach C_{MAX}; CI=Confidence interval

Table 3: Geometric mean (%CV) of Infliximab at Week 54 (PK population) –Study PLANET RA in Rheumatoid Arthritis

Parameter	n/N (%)		INFLECTRA®	REMICADE®
	INFLECTRA®	REMICADE®		
C_{MAX} (µg/mL)	221/290 (76.2)	208/288 (72.2)	75.34 (38)	69.16 (32)
T_{MAX} (h)*	221/290 (76.2)	208/288 (72.2)	2.12 (2.00, 3.18)	2.08 (1.92, 3.32)

$C_{MAX,SS}$=Maximum serum concentration at steady state; T_{MAX}=Time to reach
*T_{max} was reported as median (minimum, maximum)

CLINICAL TRIALS

Comparability of INFLECTRA® with REMICADE®

The clinical development program to show clinical comparability between INFLECTRA® and the reference product is based on

- A pivotal comparative pharmacokinetic (PK) phase 1 study (PLANET AS (CT-P13 1.1)) in 250 patients with ankylosing spondylitis (AS) of which 128 patients received INFLECTRA®.
- A pivotal comparative efficacy and safety study (PLANET RA (CT-P13 3.1) in 606 patients with rheumatoid arthritis (RA) of which 301 patients received INFLECTRA®.

A summary of the design and subject demographics of the two studies is presented in Table 4.

Table 4: Study PLANET AS and PLANET RA patient demographics and study design

STUDY	Design	Dosage, route of administration and duration	Number of patients	Mean age (range)	Gender and Race n (%)
PLANET AS	Prospective Phase 1, randomized, double-blind, multicentre, multiple single-dose intravenous infusion, parallel-group in ankylosing spondylitis	INFLECTRA® or REMICADE® 5 mg/kg bw administered as 2h intravenous infusion; at Weeks 0, 2, 6, then every 8 weeks up to 54 weeks	250	38.9 (18 to 69)	202 (80.8%) male 48 (19.2%) female 189 (75.6%) White 29 (11.6%) Asian 32 (12.8%) Other
PLANET RA	Prospective Phase 3, randomized, double blind, multicentre, multiple single dose intravenous infusion, parallel group in rheumatoid arthritis	INFLECTRA® or REMICADE® (3 mg/kg bw) administered as 2h intravenous infusion; at Weeks 0, 2, 6, then every 8 weeks up to 54 weeks, co-administered with MTX and folic acid; 54 weeks	606	48.8 (18 to 75)	105 (17.3%) male 501 (82.7%) female 442 (72.9%) White 3 (0.5%) Black 71 (11.7%) Asian 90 (14.9%) Other

PLANET RA study:

Therapeutic equivalence of INFLECTRA® and REMICADE® was demonstrated in a double-blind, randomised, multicentre, parallel-group, prospective Phase 3 study in adult patients with RA not receiving adequate response with methotrexate alone.

The primary efficacy endpoint was the proportion of patients achieving clinical response according to the ACR20 criteria at Week 30.

In the all-randomized population, the proportion of patients achieving clinical response according to the ACR20 criteria at Week 30 was similar in the INFLECTRA® and REMICADE® treatment groups (184 [60.9%] patients and 178 [58.6%] patients, respectively). The 95% CI for the estimate of treatment difference was entirely contained within the range -15% to 15% (95% CI: [-0.06, 0.10]) indicating therapeutic equivalence between the treatment groups.

Comparative efficacy of INFLECTRA® with REMICADE® throughout controlled 54 weeks was similar for ACR20, ACR50, ACR70, EULAR and DAS28 at all time-points.

Patients who received REMICADE® in the initial study (54 weeks) underwent a single way transition to INFLECTRA®. While no formal comparison of efficacy was performed during the extension phase (up to week 102), efficacy outcomes were similar for patients who transitioned from REMICADE® to INFLECTRA® and those who continued INFLECTRA®.

PLANET AS study:
The efficacy of INFLECTRA® was also demonstrated in a randomized, double-blind, multicenter, parallel-group, study designed to assess the pharmacokinetic (PK) equivalence, efficacy and safety of multiple doses of either INFLECTRA® or REMICADE® reference product (5 mg/kg) administered by a 2-hour intravenous (IV) infusion per dose in patients with active ankylosing spondylitis (AS). Although, efficacy was not a primary endpoint in this study and this study was not powered to assess efficacy, INFLECTRA® and REMICADE® treatment groups showed comparable effect in terms of efficacy with regard to ASAS20 and ASAS40 responses at Weeks 14, 30, and 54.

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

The primary endpoints were the reduction of signs and symptoms as assessed by the American College of Rheumatology (ACR) criteria (ACR20 for ATTRACT, landmark ACR-N at week 54 for ASPIRE), the prevention of structural damage and the improvement in physical function. A reduction in signs and symptoms was defined to be at least a 20% improvement (ACR20) in both tender and swollen joint counts and in 3 of the following 5 criteria: evaluator's global assessment, patient's global assessment, functional/disability measure, visual analogue pain scale and erythrocyte sedimentation rate or CRP. ACR-N uses the same criteria as the ACR20, calculated by taking the lowest percentage improvement in swollen joint count, tender joint count, and the median of the remaining 5 components of the ACR response. Structural joint damage (erosions and joint space narrowing) in both hands and feet was measured by the change from baseline in the total van der Heijde-modified Sharp score (0-440). The Health Assessment Questionnaire (HAQ; scale 0-3) was used to measure patients' average change from baseline scores over time, through week 54, in physical function.

The ATTRACT trial evaluated responses at 30 weeks (reduction in signs and symptoms), 54 weeks (the prevention of structural damage) and 102 weeks (the improvement in physical function) in a placebo-controlled study of 428 adult patients with active rheumatoid arthritis despite treatment with methotrexate. Approximately 50% of patients were in functional Class III. Patients received placebo, 3 mg/kg or 10 mg/kg infliximab at weeks 0, 2 and 6 and then every 4 or 8 weeks thereafter. All

patients were on stable methotrexate doses (median 15 mg/week) for 6 months prior to enrolment and were to remain on stable doses throughout the study.

Results from week 54 (ACR20, total van der Heijde-modified Sharp score and HAQ are shown in Table 5. Higher degrees of clinical response (ACR20, ACR50 and ACR70) were observed with infliximab versus methotrexate alone at 30 and 54 weeks compared with methotrexate alone (Table 5).

A reduction in the rate of the progression of structural joint damage (erosions and joint space narrowing) was observed in all infliximab groups at 54 weeks (Table 5).
The effects observed at 54 weeks were maintained through 102 weeks. Due to a number of treatment withdrawals, the magnitude of the effect difference between infliximab and the methotrexate alone group cannot be defined.

Table 5: Effects on ACR20, Structural Joint Damage and Physical Function at week 54, ATTRACT

	Control[a]	infliximab[b]				
		3mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8wks	10 mg/kg q 4 wks	All infliximab[b]
Patients with ACR20 response/ Patients evaluated (%)[c]	15/88 (17%)	36/86 (42%)	41/86 (48%)	51/87 (59%)	48/81 (59%)	176/340 (52%)
Total score[d] (van der Heijde-modified Sharp score)						
Change from baseline (Mean ± SD[c])	7.0 ± 10.3	1.3 ± 6.0	1.6 ± 8.5	0.2 ± 3.6	-0.7 ± 3.8	0.6 ± 5.9
Mean[c] (Interquartile range)	4.0 (0.5, 9.7)	0.5 (-1.5, 3.0)	0.1 (-2.5, 3.0)	0.5 (-1.5, 2.)	-0.5 (-3.0, 1.5)	0.0 (-1.8, 2.0)
Patients with no deterioration/patients Evaluated (%)[c]	13/64 (20%)	34/71 (48%)	35/71 (49%)	37/77 (48%)	44/66 (67%)	150/285 (53%)
HAQ change from baseline over time[e] (patients evaluated)	87	86	85	87	81	339
Mean± SD[c]	0.2 ± 0.3	0.4 ± 0.3	0.5 ± 0.4	0.5 ± 0.5	0.4 ± 0.4	0.4 ± 0.4

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

ASPIRE trial evaluated responses at 54 weeks in 1004 methotrexate naive patients with early (≤3 years disease duration) active rheumatoid arthritis. Patients randomised had a median age of 51 years with a median disease duration of 0.6 years, and median swollen and tender joint count of 19 and 31, respectively. All patients received methotrexate (optimised to 20 mg/wk by week 8) and either placebo, 3 mg/kg or 6 mg/kg infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter. Results from week 54 are shown in Table 6.
In this trial, infusions were to be administered over 2 hours for the first 3 infusions. The duration of subsequent infusions could be shortened to not less than 40 minutes in patients who did not experience serious infusion reactions. Sixty-six per cent of the patients received at least one shortened infusion of 90 minutes or less and 44% received at least one shortened infusion of 60 minutes or less.

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

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

Table 6: Effects on ACRn, Structural Joint Damage and Physical Function at week 54, ASPIRE

	Placebo+MTX	Infliximab + MTX		
		3 mg/kg	6 mg/kg	Combined
Subjects randomised	282	359	363	722
Percentage ACR improvement				
Mean ± SD[a]				
Change from baseline in total van der Heijde modified Sharp score[b]	24.8 ± 59.7	37.3 ± 52.8	42.0 ± 47.3	39.6 ± 50.1
Mean ± SD[a]	3.70 ± 9.61	0.42 ± 5.82	0.51 ± 5.55	0.46 ± 5.68
Median				
Improvement from baseline in HAQ Averaged over time from week 30 week 54[c]	0.43	0.00	0.00	0.00
Mean ± SD[d]	0.68 ± 0.63	0.80 ± 0.65	0.88 ± 0.65	0.84 ± 0.65

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

Data to support infliximab dose adjustment in rheumatoid arthritis comes from both ATTRACT and ASPIRE, as well as from the START study. START was a randomised, multicentre, double-blind, 3-arm, parallel-group safety study. In one of the arms the secondary objective was to assess the safety and efficacy of dose escalation above 3 mg/kg of infliximab in 1.5 mg/kg increments to a maximum of 9 mg/kg, given every 8 weeks in subjects with an inadequate response to 3 mg/kg at week 22 or if a flare occurred later. Results are shown in Table 7.

Table 7: Summary of responders by number of dose escalations (START)

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

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

Rheumatoid Arthritis associated anaemia

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

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

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

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

Ankylosing Spondylitis

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

In the first study (P01522), which had a 3 month double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6 (35 patients in each group). Starting at week 12, placebo patients were switched to infliximab and all patients subsequently received 5 mg/kg infliximab every 6 weeks up to week 54. After the first year of the study, 53 patients continued into an open-label extension to week 102.

At week 12, treatment with infliximab resulted in improvement in signs and symptoms, as assessed by the BASDAI, with 57% of infliximab treated patients achieving at least 50% reduction from baseline in BASDAI score, (mean baseline score was 6.5 in the infliximab group and 6.3 in the placebo group), compared to 9% of placebo patients (p<0.01). The absolute difference in the BASDAI score compared with placebo at week 12 was 2.4. At 54 and 102 weeks there were 54 and 49 subjects still on infliximab treatment and among those, 34 (63%) and 30 (61%) were BASDAI 50 responders. Improvement was observed as early as week 2, and was maintained through week 102. Physical function range of motion, and quality of life (SF-36) were improved similarly.

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

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

placebo patients (p<0.001). The median improvement from baseline in range of axial motion, as assessed by the BASMI was 1.0 for the infliximab-treated group vs. 0.0 for the placebo group (p=0.019). The median percent improvement from baseline in chest expansion was 17% for the infliximab-treated group and 0% for the placebo group (p=0.037). Physical function and quality of life as measured by the BASFI and the SF-36 were also improved significantly at week 24.

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

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

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

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

In the second trial (IMPACT 2), efficacy and safety of infliximab were studied in 200 patients with active psoriatic arthritis (≥5 swollen joints and ≥5 tender joints) with one or more of the following subtypes: arthritis involving DIP joints, arthritis mutilans, asymmetric peripheral arthritis, polyarticular arthritis, and spondylitis with peripheral arthritis. Patients also had plaque psoriasis with a qualifying target lesion ≥2 cm in diameter. Forty-six percent of patients continued on stable doses of methotrexate (≤25 mg/week). Patients had previously been treated with NSAIDs (81.5%), DMARDs (79.5%) and corticosteroids (29.0%). During the 24-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6, 14, and 22 (100 patients in each group). At week 16, placebo patients with <10% improvement from baseline in both swollen and tender joint counts were switched to infliximab induction (early escape). At week 24, all placebo-treated patients crossed over to infliximab induction. Dosing continued for all patients through week 46.

Key efficacy results for IMPACT and IMPACT 2 are shown in Table 8 below:

Table 8: Effects on ACR, PASI and Physical Function in IMPACT and IMPACT 2

	IMPACT				IMPACT 2		
	Placebo (Week 16)	Infliximab (Week 16)	Infliximab (Week 50)	Infliximab (Week 98)	Placebo (Week 24)	Infliximab (Week 24)	Infliximab (Week 54)
Patients randomized	52	52	52	N/A[a]	100	100	100
ACR response (% of patients)							
N	52	52	49	78	100	100	76
ACR20 response*	5 (10%)	34 (65%)	34 (69%)	48 (62%)	16 (16%)	54 (54%)	48 (63%)
ACR50 response*	0 (0%)	24 (46%)	26 (53%)	35 (45%)	4 (4%)	41(41%)	32 (42%)
ACR70 response*	0 (0%)	15 (29%)	19 (39%)	27 (35%)	2 (2%)	27 (27%)	20 (26%)
PASI response (% of patients)[b]							
N	16	22	22	25	87	83	61
PASI 50 response*	0 (0%)	22 (100%)	19 (86%)	19 (76%)	7 (8%)	62 (75%)	42 (69%)
PASI 75 response*	0 (0%)	15 (68%)	13 (59%)	16 (64%)	1 (1%)	50 (60%)	31 (51%)
PASI 90 response*	0 (0%)	8 (36%)	9 (41%)	12 (48%)	0 (0%)	32 (39%)	26 (43%)
HAQ (% improvement from baseline)[e]							
N	51	51	48	77	95	94	76
Mean (± SD)*	-2% (8)	50% (8)	43% (9)	38% (72)	-19% (103)	46% (42)	43% (96)

[a]Week 98 data for IMPACT includes combined placebo crossover and infliximab patients who entered the open-label extension
[b]Based on patients with PASI >2.5 at baseline for IMPACT, and patients with >3% BSA psoriasis skin involvement at baseline in IMPACT 2
[e]HAQ=Health Assessment Questionnaire
*$p \leq 0.01$for infliximab vs. placebo at week 16 in IMPACT; $P<0.001$ for infliximab vs. placebo at week 24 for IMPACT2

In IMPACT and IMPACT 2, clinical responses were observed as early as week 2 and were maintained through week 98 and week 54 respectively. The responses were similar regardless of concomitant use of methotrexate.

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

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

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

The change from baseline at weeks 24 and 54 in the total modified vdH-S score in IMPACT 2 is presented in the table below:

Table 9: Summary of change from baseline in total modified van der Heijde modified Sharp score at weeks 24 and 54 (IMPACT 2)

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

*placebo patients crossed over to infliximab at week 24

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

Psoriasis

The efficacy of infliximab was assessed in two multicentre, randomised, double blind studies: SPIRIT and EXPRESS. Patients in both studies had plaque psoriasis (Body Surface Area [BSA] ≥10% and Psoriasis Area and Severity Index [PASI] score ≥12). The primary endpoint in both studies was the percent of patients who achieved ≥75% improvement in PASI from baseline at week 10. Marked responders were identified as patients who achieved ≥90% improvement in PASI from baseline.

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

In SPIRIT, the median baseline BSA was 27.0%, the median baseline PASI score was 18.9; 62.2% of patients had a baseline PGA score of "moderate" and 24.9% of patients had a baseline PGA score of "marked" or "severe." Prior therapy with PUVA, methotrexate, cyclosporin or acitretin had been received by 81.5% of the patients. The proportion of patients with ≥75% improvement in PASI from baseline (PASI 75) at week 10 was 79.8% in the combined infliximab group, 71.7% in the 3 mg/kg infliximab group, 87.9% in the 5 mg/kg infliximab group, and 5.9% in the placebo group ($p<0.001$ for each infliximab versus placebo comparison). At week 10, a significantly greater proportion of infliximab-treated patients, both in the combined group (51.5%) and in the individual groups (3 mg/kg: 45.5%; 5 mg/kg: 57.6%), achieved a marked response (≥90% improvement in PASI from baseline) compared to the placebo-treated patients (2.0%). In the 3 mg/kg group, 60.6% of patients maintained response through week 14 and 75.3% of patients in the 5 mg/kg group maintained response through week 18. By week 26, twenty weeks after the last induction dose, 30% of patients in the 5 mg/kg group and 13.8% of patients in the 3 mg/kg group were PASI 75 responders, suggesting the need for maintenance therapy.

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

EXPRESS evaluated the efficacy of infliximab induction and maintenance therapy in 378 patients with plaque psoriasis who were candidates for phototherapy or systemic therapy. Patients received 5 mg/kg infliximab or placebo infusions at weeks 0, 2 and 6 followed by maintenance therapy every 8

weeks through week 22 in the placebo group and through week 46 in the infliximab group. At week 24, the placebo group crossed over to infliximab induction therapy (5 mg/kg) followed by infliximab maintenance therapy (5 mg/kg).

In EXPRESS, the median baseline BSA was 29%, the median baseline PASI score was 21.1 and the majority of patients (89.9%) had a PGA score of moderate, marked, or severe. Prior therapy with PUVA, methotrexate, cyclosporin, or acitretin had been received by 71.4% of patients. At week 10 PASI 75 response was achieved by 80.4% in the infliximab group vs. a placebo group rate of 2.6%, p<0.001). Median time to PASI 75 was between 2 and 6 weeks. Improvement in PASI was consistent across subgroups defined by baseline demographics, clinical disease characteristics and psoriasis medication history. Marked responses (PASI 90) at week 10 were achieved by 57.1% of the infliximab group compared to 1.3% in the placebo group (p<0.001). The response was maintained through the 24 weeks, the placebo-controlled period. PASI response rates through week 50 are presented in Table10.

Table 10: Summary of PASI Response Through Week 50 by Visit EXPRESS

	Placebo → Infliximab 5 mg/kg (at week 24)	Infliximab 5 mg/kg	P-value
Week 2			
n	77	298	
≥ 90% improvement	0 (0.0%)	3 (1.0%)	
≥ 75% improvement	0 (0.0%)	16 (5.4%)	
≥ 50% improvement	3 (3.9%)	106 (35.6%)	
Week 6			
n	77	295	
≥ 90% improvement	1 (1.3%)	94 (31.9%)	
≥ 75% improvement	4 (5.2%)	184 (62.4%)	
≥ 50% improvement	6 (7.8%)	264 (89.5%)	
Week 10			
n	77	301	
≥ 90% improvement	1 (1.3%)	172 (57.1%)	<0.001
≥ 75% improvement	2 (2.6%)	242 (80.4%)	<0.001
≥ 50% improvement	6 (7.8%)	274 (91.0%)	
Week 24			
n	77	276	
≥ 90% improvement	1 (1.3%)	161 (58.3%)	<0.001
≥ 75% improvement	3 (3.9%)	227 (82.2%)	<0.001
≥ 50% improvement	5 (6.5%)	248 (89.9%)	
Week 50			
n	68	281	
≥ 90% improvement	34 (50.0%)	127 (45.2%)	
≥ 75% improvement	52 (76.5%)	170 (60.5%)	
≥ 50% improvement	61 (89.7%)	193 (68.7%)	

At week 10, 82.9% of infliximab patients achieved a PGA score of minimal or cleared compared to 3.9% of placebo patients (p<0.001). PGA scores at weeks 6, 10, 24 and 50 are presented in Table 11.

Table 11: Summary of PGA Scores Through Week 50 by Visit, EXPRESS

	Placebo → Infliximab 5 mg/kg (at week 24)	Infliximab 5 mg/kg	P-value
Week 2			
n	77	298	
PGA of cleared (0) or minimal (1)	3 (3.9%)	59 (19.8%)	
PGA of cleared (0), minimal (1), or mild (2)	9 (11.7%)	208 (69.8%)	
Week 6			
n	77	295	
PGA of cleared (0) or minimal (1)	2 (2.6%)	205 (69.5%)	
PGA of cleared (0), minimal (1), or mild (2)	16 (20.8%)	272 (92.2%)	
Week 10			
n	77	292	
PGA of cleared (0) or minimal (1)	3 (3.9%)	242 (82.9%)	< 0.001
PGA of cleared (0), minimal (1), or mild (2)	14 (18.2%)	275 (94.2%)	< 0.001
Week 24			
n	77	276	
PGA of cleared (0) or minimal (1)	2 (2.6%)	203 (73.6%)	< 0.001
PGA of cleared (0), minimal (1), or mild (2)	15 (19.5%)	246 (89.1%)	< 0.001
Week 50			
n	68	281	
PGA of cleared (0) or minimal (1)	46 (67.6%)	149 (53.0%)	
PGA of cleared (0), minimal (1), or mild (2)	59 (86.8%)	189 (67.3%)	

The median baseline value for the DLQI was 12.5. The mean baseline values were 45.6 for the SF-36 physical component and 45.7 for the mental component. Quality of life improved significantly compared to placebo at weeks 10 and 24 when evaluated by both DLQI and SF-36.

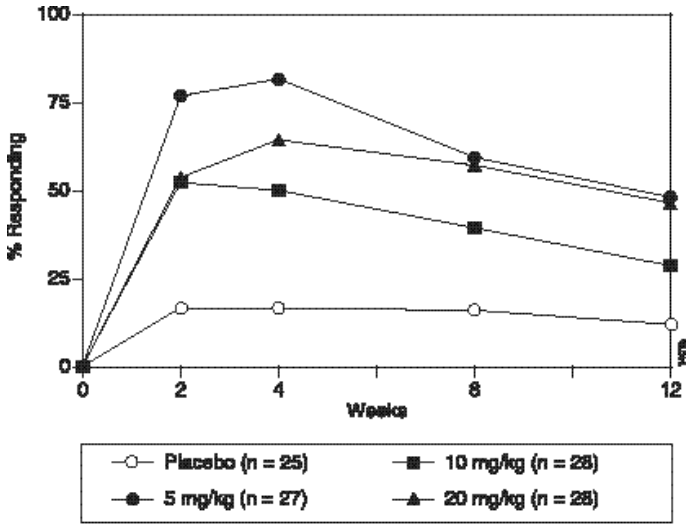
The median baseline NAPSI score for nail psoriasis was 4 and the median number of nails involved with psoriasis was 10. Patients treated with infliximab showed a clear improvement in nail psoriasis from baseline compared to placebo treated patients, as measured by NAPSI score, and by the decrease in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

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

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

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

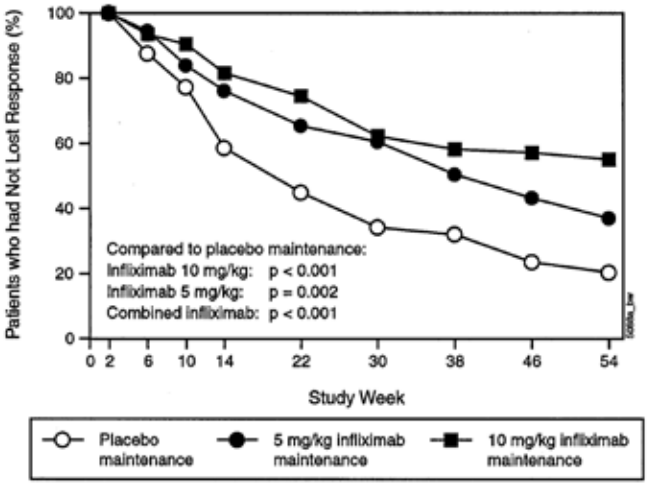
Figure 1: Response (≥70 point decrease in CDAI) to a Single IV Infliximab or Placebo Dose



In the multidose trial, 573 patients, with a score of at least CDAI 220, received 5 mg/kg at week 0. After assessment of response, patients were randomly assigned to one of three treatment groups; placebo at weeks 2 and 6 and then every 8 weeks until week 46; 5 mg/kg at weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group, which received 5 mg/kg at weeks 2 and 6, and then 10 mg/kg every 8 weeks. The prespecified co-primary endpoints were the proportion of patients who responded at week 2 and were in remission (CDAI <150) at week 30 and the time to loss of response in patients who responded. Analyses of the endpoints were on the intent to treat patient population.

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

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



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

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

In a subset of patients who participated in an endoscopic substudy, a significantly greater proportion of patients in the infliximab maintenance groups combined (10/32 patients, 31%) had healing of the mucosa compared to patients in the placebo group (0/17 patients, 0%) at week 10 ($p=0.010$). Results were similar at week 54.

Fistulising Crohn's Disease

The safety and efficacy of infliximab were assessed in a randomised, double-blind, placebo controlled study of 94 patients with fistulising Crohn's disease with fistulas that were of at least 3 months' duration. Thirty-one of these patients were treated with infliximab 5mg/kg. Approximately 93% of the patients had previously received antibiotic or immunosuppressive therapy.

Concurrent use of stable doses of conventional therapies was permitted, and 83% of patients continued to receive at least one of these medications. Fifty-two (55%) had multiple cutaneously draining fistulas, 90% of patients had fistulas in the perianal area and 10% had abdominal fistulas.

Patients received 3 doses of infliximab 5 or 10 mg/kg or placebo at Weeks 0, 2 and 6 and were followed up to 26 weeks. The primary endpoint was the proportion of patients who experienced a clinical response, defined as ≥50% reduction from baseline in the number of fistulas draining upon gentle compression, on at least two consecutive visits, without an increase in medication or surgery for Crohn's disease.

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

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

Active Crohn's disease in children and adolescent patients (6 to17 years)
The safety and efficacy of single and multiple doses of infliximab were assessed in a randomised, single-dose, multicentre Phase II study in 21 children and adolescent patients with active Crohn's disease, and in a randomised, multiple dose, open-label, multicentre Phase III study in 112 children and adolescent Crohn's disease patients (the REACH trial). In REACH, all subjects were required to be on a stable dose of 6-MP, AZA or MTX (35% were also receiving corticosteroids at baseline).

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

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

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

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

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

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

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

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

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

Ulcerative colitis

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

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

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

Table 12: Effects on clinical response, clinical remission and mucosal healing at Weeks 8 and 30. Combined data from ACT 1 & ACT 2

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects randomised	244	242	242	484
Percentage of subjects in clinical response and in sustained clinical response				
Clinical response at Week 8[a]	33.2%	66.9%	65.3%	66.1%
Clinical response at Week 30[a]	27.9%	49.6%	55.4%	52.5%
Sustained response (clinical response at both Week 8 and Week 30)[a]	19.3%	45.0%	49.6%	47.3%
Percentage of subjects in clinical remission, sustained remission, and in remission without Corticosteroids				
Clinical remission at Week 8[a]	10.2%	36.4%	29.8%	33.1%
Clinical remission at Week 30[a]	13.1%	29.8%	36.4%	33.1%
Sustained response (clinical response at both Week 8 and Week 30)[a]	5.3%	19.0%	24.4%	21.7%
Randomised subjects with corticosteroids at baseline	139	130	139	269
Subjects without corticosteroids and in clinical remission at Week 30[b]	7.2%	21.5%	23.0%	22.3%
Percentage of subjects with mucosal healing				
Mucosal healing at Week 8[a]	32.4%	61.2%	60.3%	60.7%
Mucosal healing at Week 30[a]	27.5%	48.3%	52.9%	50.6%

a: $p < 0.001$, for each infliximab treatment group vs. placebo
b: $p \leq 0.001$, for each infliximab treatment group vs. placebo

In both studies, a significantly greater percentage of patients in the infliximab groups were in clinical response and clinical remission at week 8 when compared to placebo. Furthermore, in both ACT 1 and ACT 2, a significantly greater proportion of patients treated with 5 mg/kg or 10 mg/kg infliximab experienced clinical response and clinical remission at week 30 compared to placebo treatment. In addition, the proportion of patients in sustained response (i.e., were in clinical response at both week 8 and week 30) in the infliximab groups was at least twice as large as in the placebo group. Results from weeks 8 and 30 are shown in Table 12.

Of patients treated with corticosteroids at baseline, a significantly greater proportion of patients in the infliximab-treated groups were in clinical remission at week 30 and able to discontinue corticosteroids compared to the placebo-treated patients (22.3% versus 7.2%, respectively, see Table 12).

Additionally, at weeks 8 and 30, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg dose groups in ACT 1 and ACT 2 achieved mucosal healing compared to patients in the placebo group. The proportion of subjects with mucosal healing was similar between the 2 infliximab dose groups in the two studies (see Table 12).

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

At 54 weeks, 44.9% of patients in the combined infliximab treatment group were in clinical response compared to 19.8% in the placebo treatment group ($p<0.001$). Clinical remission and mucosal healing occurred in a greater proportion of patients in the combined infliximab treatment group compared to the placebo treatment group at week 54 (34.6% vs. 16.5%, $p<0.001$ and 46.1% vs. 18.2%, $p<0.001$, respectively). The proportions of patients in sustained response and sustained remission at week 54 were greater in the combined infliximab treatment group than in the placebo treatment group (37.9% vs. 14.0%, $p<0.001$; and 20.2% vs. 6.6%, $p<0.001$, respectively).

A greater proportion of patients in the combined infliximab treatment group were able to discontinue corticosteroids while remaining in clinical remission compared to the placebo treatment group at both week 30 (22.3% vs. 7.2%, p ≤0.001, see Table 12) and week 54 (21.0% vs. 8.9%, p=0.022).

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

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

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

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

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

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

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

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

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

INDICATIONS

Rheumatoid Arthritis in adults
INFLECTRA®, in combination with methotrexate, is indicated for the reduction of signs and symptoms and prevention of structural joint damage (erosions and joint space narrowing) in:
- patients with active disease despite treatment with methotrexate
- patients with active disease who have not previously received methotrexate.

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

Ankylosing Spondylitis
INFLECTRA® is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease.

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

INFLECTRA® may be administered in combination with methotrexate.

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

Crohn's Disease in Adults and in Children and adolescents (6 to 17 years)
INFLECTRA® is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies.

Refractory Fistulising Crohn's Disease
INFLECTRA® is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.

Ulcerative colitis in Adults and in Children and adolescents (6 to 17 years)
INFLECTRA® is indicated for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy.

CONTRAINDICATIONS

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

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

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

Do not initiate therapy in patients with congestive heart failure.

PRECAUTIONS

The comparability of INFLECTRA® with REMICADE® has been demonstrated, with regard to particular physicochemical characteristics and efficacy and safety outcomes [see PHARMACOLOGY and CLINICAL TRIALS]. The level of comparability that has been shown supports the use of INFLECTRA® for the listed indications.

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

Infusion reactions and hypersensitivity reactions
Infliximab has been associated with acute infusion effects and a delayed hypersensitivity reaction. These differ in their time of onset. Therefore, all patients receiving infliximab should be observed for at least one to two hours post infusion for side effects.

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

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

Antibodies to infliximab may develop in some patients. These antibodies have been associated with an increased frequency of infusion reactions, and may be associated with an increased risk of serious infusion reactions. A low proportion of the infusion reactions were serious allergic reactions.

In Crohn’s disease patients, an association between development of antibodies to infliximab and reduced duration of response has also been observed. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and a reduction in the frequency of infusion reactions. The effect of concomitant immunomodulator therapy was more profound in episodically treated patients than in patients given maintenance therapy. Patients who are not receiving immunosuppressants during infliximab treatment are potentially at greater risk of developing these antibodies. These antibodies cannot always be detected in serum samples. If serious reactions occur, symptomatic treatment must be given and further infliximab infusions must not be administered.

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

Infusion reactions following re-administration of infliximab
In a psoriasis clinical trial, a 3-dose re-induction of infliximab after a period of no treatment resulted in a higher incidence of serious infusion reactions during the re-induction regimen (see ADVERSE EFFECTS) than had been observed in rheumatoid arthritis, psoriasis, and Crohn's disease trials in which a period of no drug treatment was followed by regular maintenance therapy without re-induction. In the case where infliximab maintenance therapy for psoriasis is interrupted, infliximab should be reinitiated as a single dose followed by maintenance therapy. In general, the benefit-risk of re-administration of infliximab after a period of no-treatment, especially as a re-induction regimen given at weeks 0, 2, and 6, should be carefully considered.

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

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

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

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

Hepatosplenic T-cell lymphomas
Rare postmarketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF-blocking agents including infliximab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were reported in adolescent or young adult males. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with or immediately prior to infliximab.

It is uncertain whether the occurrence of the HSTCL is related to infliximab or infliximab in combination with these other immunosuppressants. When treating patients with inflammatory bowel disease, particularly in adolescents and young adults, consideration of whether to use infliximab alone or in combination with other immunosuppressants should take into account a possibility that there is a

higher risk of HSTCL with combination therapy versus an observed increased risk of immunogenicity and hypersensitivity reactions with infliximab monotherapy from the clinical trial data.

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

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

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

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

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

Auto-immune processes
The relative deficiency of TNFα caused by anti-TNF therapy may result in the initiation of an autoimmune process in a subgroup of genetically susceptible patients. If drug-induced lupus is suspected, patients being treated with infliximab should have regular measurements of Antinuclear antibodies (ANA) and double-stranded DNA (dsDNA) antibodies. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with infliximab and is positive for antibodies against double-stranded DNA, treatment should be discontinued (see ADVERSE EFFECTS).

Studies have not been performed to assess the effects of infliximab on the healing of the internal fistula canal, on closure of non-cutaneously draining fistulas (e.g. entero-entero) or on cutaneously draining fistulas in locations other than perianal and periabdominal.

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

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

Caution should be exercised when considering the use of infliximab in patients with a chronic infection or a history of recurrent infection.

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

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

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

Tuberculosis
Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), has been observed in patients receiving infliximab. Patients must be evaluated for the risk of tuberculosis, including latent tuberculosis, prior to initiation of infliximab. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e. tuberculin skin test and chest x-ray, should be performed in all patients. Prescribers are reminded of the risk of false negative tuberculin skin test results especially in patients who are severely ill or immunocompromised. If active tuberculosis is diagnosed, infliximab therapy must not be initiated (see CONTRAINDICATIONS). If latent tuberculosis is diagnosed, treatment must be initiated prior to treatment with infliximab, in accordance with local recommendations. Use of anti-tuberculosis therapy should also be considered before the initiation of infliximab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients must be monitored closely for infections, including miliary tuberculosis, while on and after treatment with infliximab.

Use of anti-tuberculosis therapy should be considered before the initiation of infliximab in patients who have several or highly significant risk factors for tuberculosis infection and have a negative test for latent tuberculosis. The decision to initiate anti-tuberculosis therapy in these patients should only be made following consultation with a physician with expertise in the treatment of tuberculosis and taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy.

Cases of active tuberculosis have occurred in patients treated with infliximab during and after treatment for latent tuberculosis. Patients receiving INFLECTRA® should be monitored closely for signs and symptoms of active tuberculosis during and after treatment, including patients who tested negative for latent tuberculosis. All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g. persistent cough, wasting/weight loss, low-grade fever) appear during or after infliximab treatment.

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

In patients treated with infliximab, an invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if they develop a serious systemic illness. Invasive fungal infections may present as disseminated rather than localized disease, and antigen and antibody testing may be negative in some patients with active

infection. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. The decision to administer empiric antifungal therapy should be made, if feasible, in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of anti-fungal therapy.

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

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

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

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

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

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

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

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

Switching between Biological Therapeutics
When switching from one biologic to another, patients should continue to be monitored for signs of infection.

Neurological events
Infliximab and other agents that inhibit TNFα have been associated in rare cases with seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders including multiple sclerosis, and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barre syndrome (see ADVERSE EFFECTS). Prescribers should exercise caution in considering the use of infliximab in patients with these neurological disorders and should consider discontinuation of infliximab if these disorders develop.

Haematological Events
Cases of leukopaenia, neutropaenia, thrombocytopaenia, and pancytopaenia, some with a fatal outcome, have been reported in patients receiving TNF-blockers, including infliximab. The causal relationship to infliximab therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with infliximab who have ongoing or a history of significant haematological abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g. persistent fever) while on infliximab. Discontinuation of infliximab therapy should be considered in patients who develop significant haematological abnormalities.

Live Vaccines/Therapeutic Infectious Agents
In patients receiving anti-TNF therapy, limited data are available on the responses to vaccination or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with INFLECTRA is not recommended.

Fatal outcome due to disseminated *Bacille Calmette-Guérin* (BCG) infection has been reported in an infant who received BCG vaccine after in utero exposure to infliximab. At least a six month waiting period following birth is recommended before the administration of live vaccines to infants exposed in utero to infliximab (see Use in Pregnancy).
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 INFLECTRA®.

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

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

Treatment discontinuation should be considered in patients with stable congestive heart failure, especially in those who have not had a significant clinical response to infliximab therapy. If a decision is made to continue treatment, cardiac status should be closely monitored.

Hepatobiliary Events
Very rare cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of infliximab. Isolated cases of liver failure resulting in liver transplantation or death have occurred. A causal relationship between infliximab and these events has not been established. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or ALT elevations ≥5 times the upper limit of

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

Carcinogenicity
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of infliximab.

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

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

Use in Pregnancy (Category C)
Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

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

As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been detected in the serum of infants up to six months following birth.. After in utero exposure to infliximab, infants may be at increased risk of infection, including disseminated infection that can become fatal ((see PRECAUTIONS, Vaccinations).

Because infliximab does not cross react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted. In a developmental toxicity study conducted in mice using an analogous monoclonal antibody that selectively inhibits the functional activity of mouse TNFα, no evidence of maternal toxicity, embryotoxicity or teratogenicity was observed.

Use during Lactation
Infliximab is not recommended for use during lactation. It is not known if infliximab is excreted in human milk or absorbed systemically after ingestion by the infant.
Breastfeeding should be discontinued for at least 6 months after infliximab treatment.

Use in Children and adolescents (6-17 years)
Treatment with infliximab has not been studied in children and adolescent patients ≤17 years with ankylosing spondylitis, psoriatic arthritis or plaque psoriasis. Treatment with infliximab has not been studied in paediatric patients with ulcerative colitis or Crohn's disease under the age of 6 years. Until safety and efficacy data in the above mentioned groups of paediatric patents are available, such

treatment is to be avoided. It should be noted that all children and adolescent patients in the Phase 3 trial in Crohn's disease (REACH) were required to be on a stable dose of either 6-MP, AZA or MTX.

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

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

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

Interactions with other Medicines
While specific studies on drug interactions with infliximab have not been conducted, the majority of patients in clinical trials received concomitant medications normally used in Crohn's disease. These medications included antibiotics, (including antiviral agents), corticosteroids, 6-mercaptopurine/azathioprine and aminosalicylates. No interactions were reported. Because corticosteroids alter electrolyte balance and fluid retention, the volume of distribution of infliximab was greater in patients taking corticosteroids. However no significant clinical sequelae were apparent.

In rheumatoid arthritis, psoriatic arthritis and Crohn's disease patients, there are indications that concomitant use of methotrexate and other immunomodulators reduces the formation of antibodies against infliximab and increases the plasma concentrations of infliximab. However, the results are uncertain due to limitations in the methods used for serum analyses of infliximab and antibodies against infliximab. Corticosteroids do not appear to affect the pharmacokinetics of infliximab to a clinically relevant extent (See ADVERSE EFFECTS; Immunogenicity).

In psoriasis, concomitant use of infliximab with other immunosuppressive agents has not been studied (see PRECAUTIONS).

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

Concurrent use of infliximab with other Biological Therapeutics
The combination of infliximab with other biological therapeutics used to treat the same conditions as infliximab, including anakinra or abatacept is not recommended (see PRECAUTIONS).

Live Vaccines/Therapeutic Infectious Agents
It is recommended that live vaccines not be given concurrently with INFLECTRA®. It is also recommended that live vaccines not be given to infants after in utero exposure to infliximab for at least 6 months following birth. (see PRECAUTIONS).

It is recommended that therapeutic infectious agents not be given concurrently with INFLECTRA® (see PRECAUTIONS).

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

ADVERSE EFFECTS

Comparability of INFLECTRA® with REMICADE®
In both clinical studies conducted, INFLECTRA® was well tolerated, and the safety profile of INFLECTRA® was similar to that of REMICADE®.

During clinical studies, 621 patients with rheumatoid arthritis and 250 patients with ankylosing spondylitis were exposed to infliximab. The safety profile of infliximab observed in these clinical studies was consistent with that previously reported for the reference product used in these studies.

The pattern of treatment-emergent adverse events and serious adverse events was comparable between treatment groups in both controlled and extension studies and was consistent with the safety profile of REMICADE®.

Table 13: Study PLANET RA Treatment-Emergent Adverse Events Reported for at Least 1% of Rheumatoid Arthritis Patients in Either Treatment Group by System Organ Class and preferred Term: Safety Population

System Organ Class Preferred Term	INFLECTRA® 3 mg/kg (N = 302)	REMICADE® 3 mg/kg (N = 300)	Total (N = 602)
	Number (%) of patients		
Total number of TEAEs	715	722	1437
Number (%) of patients with at least 1 TEAE	212 (70.2)	211 (70.3)	423 (70.3)
Blood and lymphatic system disorders			
Anemia	10 (3.3)	12 (4.0)	22 (3.7)
Leukopenia	1 (0.3)	5 (1.7)	6 (1.0)
Neutropenia	3 (1.0)	2 (0.7)	5 (0.8)
Cardiac disorders			
Atrial fibrillation	0	3 (1.0)	3 (0.5)
Sinus bradycardia	0	3 (1.0)	3 (0.5)
Ear and labyrinth disorders			
Vertigo	3 (1.0)	0	3 (0.5)
Eye disorders			
Cataract	5 (1.7)	1 (0.3)	6 (1.0)
Gastrointestinal disorders			
Abdominal pain	4 (1.3)	3 (1.0)	7 (1.2)
Abdominal pain upper	3 (1.0)	3 (1.0)	6 (1.0)
Dental caries	3 (1.0)	1 (0.3)	4 (0.7)
Diarrhea	8 (2.6)	8 (2.7)	16 (2.7)
Gastritis	1 (0.3)	6 (2.0)	7 (1.2)
Gastroesophageal reflux disease	1 (0.3)	4 (1.3)	5 (0.8)
Nausea	1 (0.3)	4 (1.3)	5 (0.8)
Peptic ulcer	3 (1.0)	0	3 (0.5)
Vomiting	0	3 (1.0)	3 (0.5)
General disorders and administration site conditions			
Asthenia	3 (1.0)	1 (0.3)	4 (0.7)

System Organ Class Preferred Term	INFLECTRA® 3 mg/kg (N = 302)	REMICADE® 3 mg/kg (N = 300)	Total (N = 602)
	Number (%) of patients		
Total number of TEAEs	715	722	1437
Number (%) of patients with at least 1 TEAE	212 (70.2)	211 (70.3)	423 (70.3)
Infusion-related reaction	10 (3.3)	11 (3.7)	21 (3.5)
Edema peripheral	3 (1.0)	1 (0.3)	4 (0.7)
Pyrexia	2 (0.7)	11 (3.7)	13 (2.2)
Immune system disorders			
Anaphylactic reaction	3 (1.0)	1 (0.3)	4 (0.7)
Drug hypersensitivity	6 (2.0)	11 (3.7)	17 (2.8)
Hypersensitivity	2 (0.7)	4 (1.3)	6 (1.0)
Infections and infestations			
Bronchitis	13 (4.3)	17 (5.7)	30 (5.0)
Cellulitis	4 (1.3)	1 (0.3)	5 (0.8)
Gastroenteritis	7 (2.3)	8 (2.7)	15 (2.5)
Herpes zoster	3 (1.0)	5 (1.7)	8 (1.3)
Influenza	11 (3.6)	5 (1.7)	16 (2.7)
Latent tuberculosis	27 (8.9)	25 (8.3)	52 (8.6)
Nasopharyngitis	24 (7.9)	17 (5.7)	41 (6.8)
Oral herpes	2 (0.7)	6 (2.0)	8 (1.3)
Pharyngitis	7 (2.3)	9 (3.0)	16 (2.7)
Pneumonia	5 (1.7)	1 (0.3)	6 (1.0)
Respiratory tract infection viral	5 (1.7)	1 (0.3)	6 (1.0)
Rhinitis	4 (1.3)	9 (3.0)	13 (2.2)
Tonsillitis	1 (0.3)	3 (1.0)	4 (0.7)
Tooth abscess	1 (0.3)	5 (1.7)	6 (1.0)
Upper respiratory tract infection	27 (8.9)	16 (5.3)	43 (7.1)
Urinary tract infection	18 (6.0)	21 (7.0)	39 (6.5)
Injury, poisoning, and procedural complications			
Contusion	6 (2.0)	2 (0.7)	8 (1.3)
Investigations			
Alanine aminotransferase increased	15 (5.0)	17 (5.7)	32 (5.3)
Aspartate aminotransferase increased	6 (2.0)	9 (3.0)	15 (2.5)
Blood creatine phosphokinase increased	4 (1.3)	7 (2.3)	11 (1.8)
Blood pressure increased	3 (1.0)	3 (1.0)	6 (1.0)
Body temperature increased	1 (0.3)	3 (1.0)	4 (0.7)
Gamma-glutamyltransferase increased	5 (1.7)	4 (1.3)	9 (1.5)
Hepatic enzyme increased	7 (2.3)	2 (0.7)	9 (1.5)
Transaminases increased	4 (1.3)	5 (1.7)	9 (1.5)
Weight increased	0	3 (1.0)	3 (0.5)
Metabolism and nutrition disorders			
Hypokalemia	4 (1.3)	3 (1.0)	7 (1.2)
Musculoskeletal and connective tissue disorders			
Arthralgia	5 (1.7)	4 (1.3)	9 (1.5)
Back pain	4 (1.3)	4 (1.3)	8 (1.3)
Bone pain	4 (1.3)	2 (0.7)	6 (1.0)

System Organ Class Preferred Term	INFLECTRA® 3 mg/kg (N = 302)	REMICADE® 3 mg/kg (N = 300)	Total (N = 602)
	Number (%) of patients		
Total number of TEAEs	715	722	1437
Number (%) of patients with at least 1 TEAE	212 (70.2)	211 (70.3)	423 (70.3)
Muscle spasms	1 (0.3)	3 (1.0)	4 (0.7)
Osteoarthritis	5 (1.7)	2 (0.7)	7 (1.2)
Rheumatoid arthritis	15 (5.0)	11 (3.7)	26 (4.3)
Nervous system disorders			
Dizziness	2 (0.7)	3 (1.0)	5 (0.8)
Headache	13 (4.3)	16 (5.3)	29 (4.8)
Migraine	0	4 (1.3)	4 (0.7)
Psychiatric disorders			
Anxiety	2 (0.7)	3 (1.0)	5 (0.8)
Renal and urinary disorders			
Dysuria	3 (1.0)	1 (0.3)	4 (0.7)
Hematuria	3 (1.0)	4 (1.3)	7 (1.2)
Reproductive system and breast disorders			
Metrorrhagia	1 (0.3)	3 (1.0)	4 (0.7)
Respiratory, thoracic, and mediastinal disorders			
Cough	6 (2.0)	1 (0.3)	7 (1.2)
Epistaxis	3 (1.0)	0	3 (0.5)
Oropharyngeal pain	5 (1.7)	4 (1.3)	9 (1.5)
Skin and subcutaneous tissue disorders			
Dermatitis allergic	1 (0.3)	3 (1.0)	4 (0.7)
Psoriasis	3 (1.0)	0	3 (0.5)
Rash	5 (1.7)	6 (2.0)	11 (1.8)
Vascular disorders			
Hypertension	15 (5.0)	10 (3.3)	25 (4.2)

Note: The total number of treatment-emergent adverse events count included all patient events. At each level of summarization, a patient was counted once if he or she reported 1 or more events. Only the most severe event was counted.
Medical Dictionary for Regulatory Activities Version 13.1 was used.

Table 14: Study PLANET AS Treatment-Emergent Adverse Events Reported for at Least 1% of Ankylosing Spondylitis Patients in Either Treatment Group by System Organ Class and Preferred Term: Safety Population

System Organ Class Preferred Term	INFLECTRA® 5 mg/kg (N = 128)	REMICADE® 5 mg/kg (N = 122)	Total (N = 250)
	Number (%) of patients		
Total number of TEAEs	350	365	715
Number (%) of patients with at least 1 TEAE	93 (72.7)	82 (67.2)	175 (70.0)
Blood and lymphatic system disorders			
Anemia	1 (0.8)	4 (3.3)	5 (2.0)
Leukopenia	0	2 (1.6)	2 (0.8)
Neutropenia	4 (3.1)	5 (4.1)	9 (3.6)
Cardiac disorders			
Bradycardia	1 (0.8)	2 (1.6)	3 (1.2)
Eye disorders			
Conjunctivitis	3 (2.3)	4 (3.3)	7 (2.8)
Uveitis	0	3 (2.5)	3 (1.2)
Gastrointestinal disorders			
Abdominal pain	1 (0.8)	3 (2.5)	4 (1.6)
Diarrhea	6 (4.7)	1 (0.8)	7 (2.8)
Dyspepsia	3 (2.3)	1 (0.8)	4 (1.6)
Gastritis	3 (2.3)	3 (2.5)	6 (2.4)
Gastroesophageal reflux disease	1 (0.8)	2 (1.6)	3 (1.2)
Nausea	4 (3.1)	2 (1.6)	6 (2.4)
Toothache	2 (1.6)	1 (0.8)	3 (1.2)
Vomiting	2 (1.6)	1 (0.8)	3 (1.2)
General disorders and administration site conditions			
Fatigue	0	2 (1.6)	2 (0.8)
Infusion-related reaction	0	4 (3.3)	4 (1.6)
Pyrexia	3 (2.3)	2 (1.6)	5 (2.0)
Hepatobiliary disorders			
Hypertransaminasemia	2 (1.6)	1 (0.8)	3 (1.2)
Immune system disorders			
Drug hypersensitivity	2 (1.6)	3 (2.5)	5 (2.0)
Infections and infestations			
Bacteriuria	1 (0.8)	3 (2.5)	4 (1.6)
Bronchitis	2 (1.6)	4 (3.3)	6 (2.4)
Cervicitis	0	2 (1.6)	2 (0.8)
Herpes simplex	2 (1.6)	1 (0.8)	3 (1.2)
Influenza	2 (1.6)	6 (4.9)	8 (3.2)
Latent tuberculosis	8 (6.3)	5 (4.1)	13 (5.2)
Nasopharyngitis	12 (9.4)	10 (8.2)	22 (8.8)
Oral herpes	1 (0.8)	2 (1.6)	3 (1.2)
Pharyngitis	4 (3.1)	7 (5.7)	11 (4.4)
Respiratory tract infection	2 (1.6)	0	2 (0.8)
Rhinitis	1 (0.8)	2 (1.6)	3 (1.2)
Sinusitis	4 (3.1)	2 (1.6)	6 (2.4)

System Organ Class Preferred Term	INFLECTRA® 5 mg/kg (N = 128) Number (%) of patients	REMICADE® 5 mg/kg (N = 122)	Total (N = 250)
Tinea pedis	2 (1.6)	1 (0.8)	3 (1.2)
Tonsillitis	0	2 (1.6)	2 (0.8)
Upper respiratory tract infection	10 (7.8)	13 (10.7)	23 (9.2)
Urinary tract infection	8 (6.3)	1 (0.8)	9 (3.6)
Viral upper respiratory tract infection	2 (1.6)	1 (0.8)	3 (1.2)
Investigations			
Alanine aminotransferase increased	19 (14.8)	19 (15.6)	38 (15.2)
Aspartate aminotransferase increased	16 (12.5)	13 (10.7)	29 (11.6)
Blood creatine phosphokinase increased	8 (6.3)	5 (4.1)	13 (5.2)
Blood lactate dehydrogenase increased	2 (1.6)	1 (0.8)	3 (1.2)
Blood phosphorus decreased	2 (1.6)	0	2 (0.8)
Gamma-glutamyltransferase increased	4 (3.1)	7 (5.7)	11 (4.4)
Hepatic enzyme increased	0	3 (2.5)	3 (1.2)
Transaminases increased	2 (1.6)	0	2 (0.8)
Weight increased	2 (1.6)	1 (0.8)	3 (1.2)
Musculoskeletal and connective tissue disorders			
Ankylosing spondylitis	5 (3.9)	3 (2.5)	8 (3.2)
Arthralgia	3 (2.3)	3 (2.5)	6 (2.4)
Back pain	3 (2.3)	4 (3.3)	7 (2.8)
Muscle spasms	2 (1.6)	0	2 (0.8)
Musculoskeletal chest pain	0	2 (1.6)	2 (0.8)
Pain in extremity	2 (1.6)	0	2 (0.8)
Temporomandibular joint syndrome	2 (1.6)	0	2 (0.8)
Nervous system disorders			
Carpal tunnel syndrome	2 (1.6)	1 (0.8)	3 (1.2)
Dizziness	4 (3.1)	1 (0.8)	5 (2.0)
Headache	10 (7.8)	7 (5.7)	17 (6.8)
Psychiatric disorders			
Depressed mood	2 (1.6)	2 (1.6)	4 (1.6)
Renal and urinary disorders			
Hematuria	0	2 (1.6)	2 (0.8)
Respiratory, thoracic, and mediastinal disorders			
Cough	2 (1.6)	1 (0.8)	3 (1.2)
Dysphonia	0	2 (1.6)	2 (0.8)
Oropharyngeal pain	3 (2.3)	2 (1.6)	5 (2.0)
Rhinitis allergic	1 (0.8)	3 (2.5)	4 (1.6)
Rhinorrhea	2 (1.6)	0	2 (0.8)
Skin and subcutaneous tissue disorders			
Dermatitis allergic	1 (0.8)	3 (2.5)	4 (1.6)
Pruritus	3 (2.3)	0	3 (1.2)
Pruritus generalized	2 (1.6)	0	2 (0.8)
Psoriasis	1 (0.8)	2 (1.6)	3 (1.2)
Rash	1 (0.8)	5 (4.1)	6 (2.4)
Seborrheic dermatitis	2 (1.6)	0	2 (0.8)

System Organ Class Preferred Term	INFLECTRA® 5 mg/kg (N = 128)	REMICADE® 5 mg/kg (N = 122)	Total (N = 250)
	Number (%) of patients		
Urticaria	0	2 (1.6)	2 (0.8)
Vascular disorders			
Hypertension	4 (3.1)	1 (0.8)	5 (2.0)

Note: The total number of treatment-emergent adverse events count included all patient events. At each level of summarization, a patient was counted once if he or she reported 1 or more events. Only the most severe event was counted.
Medical Dictionary for Regulatory Activities Version 13.1 was used.

The incidence rates of adverse events of infections in controlled and extension studies with INFLECTRA are summarised in Table 15.

Table 15: Summary of Patients reporting Infections and Serious Infection in the INFLECTRA® Clinical Studies

System Organ Class Preferred Term	All reported cases			
	Controlled Studies (Studies CT-P13 1.1, 1.2, 3.1, 3.3)		Extension Studies (Studies CT-P13 1.3, 1.2 Phase II, 3.2)	
	INFLECTRA® (N=446) n/N (%)	REMICADE® (N=440) n/N (%)	INFLECTRA® Maintenance (N=257) n/N (%)	INFLECTRA® Switch (N=235) n/N (%)
No. of patients with at least one TEAE with infections	189/446 (42.4%)	193/440 (43.9%)	74/257 (28.8%)	78/235 (33.2)
No. of patients with at least one SAE with infections	16/446 (3.6%)	10/440 (2.3%)	6/257 (2.3%)	5/235 (2.1%)
No. of SAE with infections (events)	19	12	6	5
Tuberculosis	6/446 (1.3%)	1/440 (0.2%)	1/257 (0.4%)	1/235 (0.4%)
Pneumonia	5/446 (1.1%)	0/440 (0%)	1/257 (0.4%)	0/235 (0%)
Sepsis	1/446 (0.2%)	2/440 (0.5%)	0/257 (0%)	1/235 (0.4%)
Other infections	6/446 (1.3%)	9/440 (2.0%)	4/257 (1.6%)	3/235 (1.3%)

SAE: serious adverse event, TEAE: treatment-emergent adverse event

In extension studies following a single-way transition from REMICADE® to INFLECTRA® in patients with rheumatoid arthritis and ankylosing spondylitis who were treated with INFLECTRA and REMICADE® for 54 weeks in controlled studies CT-P13 1.1 and CT-P13 3.1, the safety and immunogenicity profile remained consistent and similar between patients who were switched on INFLECTRA® and those who were maintained on INFLECTRA®.

In patients with RA who continued up to Week 102, treatment-emergent infections were reported in 50 (31.4%) patients continuing INFLECTRA and in 47 (32.9%) patients who were switched to INFLECTRA. Latent TB occurred in 10 (6.3%) patients in the maintenance group vs. 5 (3.5%) in the switch group. GI disorders were 10.1% in the INFLECTRA maintenance group vs 8.4% in the switch group.

In patients with AS who continued up to Week 102, treatment-emergent infections were reported in 23 (25.6%) subjects continuing INFLECTRA and in 29 (34.5%) subjects switched to INFLECTRA. The numerical difference was mainly due to TEAEs of latent TB: 4 (4.4%) vs. 7 (8.3%). GI disorders were 4.4% in the INFLECTRA maintenance group vs 14.3% in the switch group.

In clinical trials with infliximab, adverse drug reactions (ADRs) reasonably attributable to treatment were observed in 36% of placebo-treated patients and 57% of infliximab-treated patients. Reasonably-related ADRs are listed in Table 16 by system organ class and frequency. Frequency is based on the excess incidence of the ADR compared with placebo in pooled data from clinical trials involving 227 patients receiving placebo and 1421 patients receiving infliximab (Crohn's disease and rheumatoid arthritis). Most ADRs were mild to moderate in severity. Infusion-related reactions were the most common adverse reactions reported in clinical studies. The most common reason for discontinuation of treatment was infusion-related reactions (dyspnoea, urticaria, hypotension, flushing and headache).

Table 16: Undesirable effects in clinical trials (common >1/100, <1/10; uncommon >1/1000, <1/100; rare <1/1000)

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

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

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

Children and adolescent patients

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

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

The following adverse events were reported more commonly in 103 children and adolescent Crohn's disease patients randomised at week 10 administered 5 mg/kg infliximab through 54 weeks (out of a total of 112 patients who entered the REACH trial, see also CLINICAL TRIALS section) than in adult Crohn's disease patients receiving a similar treatment regimen (ACCENT 1 trial, see also CLINICAL TRIALS section): anaemia (10.7%), blood in stool (9.7%), leukopaenia (8.7%), flushing (8.7%), viral infection (7.8%), neutropaenia (6.8%), bone fracture (6.8%), bacterial infection (5.8%), and respiratory tract allergic reaction (5.8%).

Infusion-related reactions

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

Immunogenicity

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

Infections

Infections were reported in 56.3% of randomised children and adolescent subjects treated with infliximab (REACH trial), and in 50.4% of subjects in adult's Crohn's (ACCENT 1 trial).
In the REACH trial, infections were reported more frequently for subjects who received 8-weekly as opposed to 12-weekly infusions (73.6% and 38.0%, respectively), while serious infections were

reported for 3 subjects in the q8 week and 4 subjects in the 12-weekly maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported in 3 patients, 2 in the 8-weekly and 1 in the 12-weekly maintenance treatment groups. Herpes zoster was reported in 2 patients in the 8-weekly maintenance treatment group.

Paediatric ulcerative colitis (children and adolescents (6-17 years)
Overall proportions of patients with adverse events and serious adverse events were generally consistent in the paediatric ulcerative colitis and adult ulcerative colitis (ACT 1 and ACT 2) studies. In the paediatric ulcerative colitis study (C0168T72), the most common adverse event was worsening of ulcerative colitis, the incidence of which was higher in patients on the every 12 week vs. the every 8 week dosing regimen. In ACT 1 and ACT 2 studies, the most common adverse event was headache. The most common serious adverse event across these three studies was worsening of ulcerative colitis.

Infections
Infections were reported in 31 (51.7%) of 60 treated patients in C0168T72 and 22 (36.7%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in C0168T72 was similar to that in the paediatric Crohn's disease study (REACH) but higher than the proportion in the adults ulcerative colitis studies (ACT 1 and ACT 2). Unlike REACH, in which infections were reported more frequently for patients who received every 8 week as opposed to every 12 week infusions; in C0168T72, the overall incidence of infections was similar in the every 8 week (13/22 [59.1%]) and every 12 week (14/23 [60.9%] maintenance treatment groups. In C0168T72, serious infections were reported for 3 of 22 (13.6%) patients in the every 8 week and 3 of 23 (13.0%) patients in the every 12 week maintenance treatment group. Upper respiratory tract infection (7/60 [11.7%]) and pharyngitis (5/60 [8.3%]) were the most frequently reported respiratory infections among all treated patients. The infections occurring in more than one patient in a treatment group that required antimicrobial treatment were pharyngitis (4/60 [6.7%]), urinary tract infection (4/60 [6.7%]), and bronchitis (2/60 [3.3%]).

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

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

Post-marketing Experience:
During post-marketing experience, a rare type of hepatosplenic T-cell lymphoma has been reported in patients with Crohn’s disease or ulcerative colitis treated with infliximab, the majority of whom were adolescent or young adult males (see PRECAUTIONS).

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

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

serious infusion reactions). In the 6 mg/kg group, 2 out of 57 patients had a serious infusion reaction, one of whom had a possible anaphylactic reaction.

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

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

Table 17: Undesirable effects in post-marketing reports (common >1/100, <1/10; uncommon >1/1000, <1/100; rare <1/1000; very rare <1/10,000)

Neurological events		
	Rare:	Central nervous system demyelinating disorders (such as multiple sclerosis and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), neuropathies, numbness, tingling, seizure
	Very rare:	Transverse myelitis
Blood		
	Rare:	Pancytopaenia, agranolucytosis (including infants exposed in utero to infliximab).
	Very rare:	Haemolytic anaemia, idiopathic thrombocytopaenic purpura, thrombotic thrombocytopaenic purpura
Liver and biliary system		
	Rare:	Hepatitis, hepatitis B reactivation, jaundice, autoimmune hepatitis, liver failure
	Very rare:	Hepatocellular damage, Hepatosplenic T-cell lymphoma (primarily in adolescents and young adults with Crohn's disease and ulcerative colitis)
Cardiovascular system		
	Very rare:	Pericardial effusion
Body as a whole-general		
	Common:	Infusion-related reactions
	Uncommon:	Anaphylactic reactions
	Rare:	Anaphylactic shock, cutaneous and systemic vasculitis
Resistance mechanism		
	Rare:	opportunistic infections such as atypical mycobacteria, tuberculosis, pneumocystis carinii pneumonia (PCP), histoplasmosis, coccidioidomycosis, cryptococcosis, aspergillosis, listeriosis, and candidiasis, *and vaccine breathrough infection (after in utero) exposure to infliximab)
	Very rare:	Salmonellosis
Respiratory	Rare:	Interstitial pneumonitis/fibrosis
Neoplasm benign and malignant	Rare:	Melanoma
	Very rare:	Merkel cell carcinoma
	Frequency unknown:	Basal cell carcinoma, squamous cell carcinoma

***** including bovine tuberculosis [disseminated BCG infection (see PECAUTIONS – Live Vaccines/Therapeutic Infectious Agents)].

Post-marketing reports: In postmarketing spontaneous reporting, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, paediatric malignancy, and leukaemia have been reported

rarely or very rarely. Exceedingly rare cases of transient visual loss and myocardial ischaemia/myocardial infarction occurring during or within 2 hours of infliximab infusion have also been reported. In addition, interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis) has been rarely observed, which in some cases may be very rarely rapidly aggressive.

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

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

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

In the ASPIRE study, 66% of the patients (686 out of 1040) received at least one shortened infusion of 90 minutes or less and 44% of the patients (454 out of 1040) received at least one shortened infusion of 60 minutes or less. Of the infliximab-treated patients who received at least one shortened infusion, infusion-related reactions occurred in 15% of the patients and serious infusion reactions occurred in 0.4% of the patients.

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

Post-marketing surveillance has noted exceedingly rare cases of transient visual loss and myocardial ischemia/myocardial infarction occurring during or within 2 hours of infliximab infusion.

Infusion reactions following re-administration of infliximab
In rheumatoid arthritis, Crohn’s disease, and psoriasis clinical trials, re-administration of infliximab after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment.

In a clinical trial of patients with moderate to severe psoriasis designed to assess the efficacy and safety of long-term maintenance therapy versus re-treatment with an induction cycle of infliximab, 4% (8/219) of patients in the intermittent therapy arm experienced serious infusion reactions versus <1% (1/222) in the maintenance therapy arm. Patients enrolled in this trial did not receive any concomitant immunosuppressant therapy. Intermittent therapy in this trial was defined as the re-administration of an induction cycle (maximum of four infusions at 0, 2, 6, and 14 weeks) of infliximab upon disease flare after a period of no treatment. In this study, the majority of serious infusion reactions occurred during the second infusion at Week 2. Symptoms included, but were not limited to, dyspnoea, urticaria, facial oedema, and hypotension. In all cases, infliximab treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed Hypersensitivity
In a clinical study of 41 patients retreated with a liquid formulation of infliximab, which is no longer in use, following a 2 to 4 year period without infliximab treatment, 10 patients experienced undesirable effects manifesting 3 to 12 days following infusion. In 6 of these patients, the effects were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash. Some patients also experienced pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and/or headache. The clinical data are not adequate to determine if occurrence of these reactions is due to the different formulations administered to these patients in this study. Patients' signs and symptoms improved substantially or resolved with treatment in all cases. There are insufficient data on the incidence of these events after drug-free intervals of 1 to 2 years. These events have been observed only infrequently in clinical studies and post-marketing surveillance with retreatment intervals up to 1 year. In the Phase III psoriasis study, 1% (4/366) of patients experienced symptoms of arthralgia, myalgia, fever and rash early in the treatment course following infliximab infusions.

Immunogenicity
Patients who developed antibodies to infliximab were more likely to develop infusion-related reactions. In clinical studies using single and multiple infliximab doses ranging from 1 to 20 mg/kg, antibodies to infliximab were detected in approximately 24% of patients with any immunosuppressant therapy, and in approximately 37% of patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, approximately 8% of patients developed antibodies to infliximab. In psoriatic arthritis patients who received 5 mg/kg with and without methotrexate, antibodies occurred overall in 15% of patients (antibodies occurred in 4% of patients receiving methotrexate and in 26% of patients not receiving methotrexate at baseline). Of Crohn's disease patients who received maintenance treatment, approximately 6-13% developed antibodies to infliximab. The antibody incidence was 2-3 fold higher for patients treated episodically. Due to methodological shortcomings, a negative assay did not exclude the presence of antibodies to infliximab. Some patients who developed high titres of antibodies to infliximab had evidence of reduced efficacy. In a Phase III psoriasis study in which patients were treated with infliximab induction followed by every 8-week maintenance infusions without concomitant immunosuppressive therapy, antibodies were detected in approximately 20% of patients.

Comparability of INFLECTRA® with REMICADE®

In clinical studies comparing INFLECTRA® with REMICADE®, the number of patients who developed antibodies to infliximab was similar in both treatment groups at each study point. The immunogenicity following single way transition from REMICADE® to INFLECTRA® in patients with rheumatoid arthritis and ankylosing spondylitis was similar and consistent throughout extension studies (up to 102 week). In the AS study, anti-drug antibodies (ADA) were detected at Week 102 in 21/90 (23.3%) subjects continuing INFLECTRA® and in 23/84 (27.4%) subjects switched to INFLECTRA®. In the RA study anti-drug antibodies (ADA) were detected at Week 102 in 64/159 (40.3%) subjects continuing INFLECTRA® and in 64/143 (44.8%) subjects switched to INFLECTRA®.

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

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

In postmarketing spontaneous reporting, infections are the most common serious adverse event. Some of the cases have resulted in fatal outcome. Cases of tuberculosis, sometimes fatal, including miliary tuberculosis and tuberculosis with extrapulmonary location (see PRECAUTIONS), and protozoal infections have been reported rarely or very rarely.

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

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

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

In the controlled portions of some clinical trials of the TNF-blocking agents, more cases of non-lymphoma malignancy have been observed among patients receiving a TNF-blocker compared with control patients. In an exploratory clinical trial evaluating the use of infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in infliximab-treated patients compared with control patients, 5.7% [95% CI 2.65% - 10.6%] vs. 1% [95% CI 0.03% - 7.0%]. The malignancies were mainly lung and head and neck. All patients had a history of heavy smoking.

During postmarketing experience, a rare type of hepatosplenic T-cell lymphoma has been reported in adolescent and young adult patients with Crohn's disease treated with infliximab (see PRECAUTIONS – Malignancies and lymphoproliferative disorders).

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

Autoantibodies / Lupus-like Syndrome
In clinical studies approximately 52% of (1261) infliximab-treated patients who were ANA negative at baseline developed a positive ANA during the trial (compared with approximately 19% of 129

placebo-treated patients). Anti-dsDNA antibodies developed in approximately 17% (261) of patients treated with infliximab (compared with 0% of 162 placebo-treated patients. At the last evaluation, 150 of these 261 infliximab-treated patients (57%) remained anti-dsDNA positive. Clinical signs consistent with a lupus-like syndrome remain uncommon.

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

In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving infliximab without progression to severe hepatic injury. Elevations of ALT ≥5 x ULN have been observed (see Table 18). Elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving infliximab than in controls, both when infliximab was given as monotherapy and when it was used in combination with other immunosuppressive agents. Most aminotransferase abnormalities were transient; however, a small number of patients experienced more prolonged elevations. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of infliximab, or modification of concomitant medications.

Table 18: Proportion of patients with increased ALT activity in Clinical Trials

Indication	Number of patients evaluated for ALT		Median follow-up (wks)[3]		≥3 x ULN		≥5 x ULN	
	placebo	infliximab	placebo	infliximab	placebo	infliximab	placebo	infliximab
Rheumatoid arthritis[1]	375	1087	58.1	58.3	3.2%	3.9%	0.8%	0.9%
Crohn's disease[2]	173	703	54.1	54.1	3.5%	5.1%	0.0%	1.7%
Paediatric Crohn's disease	N/A	139	N/A	53.0	N/A	4.4%	N/A	1.5%
Ulcerative colitis	242	482	30.1	30.8	1.2%	2.5%	0.4%	0.6%
Ankylosing spondylitis	76	275	24.1	101.9	0.0%	9.5%	0.0%	3.6%
Psoriatic arthritis	98	191	18.1	39.1	0.0%	6.8%	0.0%	2.1%
Plaque psoriasis	281	1175	16.1	50.1	0.4%	7.7%	0.0%	3.4%

[1] Placebo patients received methotrexate while infliximab patients received both infliximab and methotrexate.
[2] Placebo patients in the 2 Phase III trials in Crohn's disease, ACCENT I and ACCENT II, received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patients who were randomised to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in the ALT analysis.
[3] Median follow-up is based on patients treated.

Table 19 and Table 20 shows the proportion of patients with elevated ALT and AST in INFLECTRA® Clinical Trials

Table 19: Proportion of Patients with Elevated ALT in INFLECTRA® Clinical Trials

	Proportion of patients with elevated ALT											
	INFLECTRA® [2]						REMICADE®[3]					
	Lowest results[1]			Highest results[1]			Lowest results[1]			Highest results[1]		
	Grade 1	Grade 2-4	Grade 3-4	Grade1	Grade 2-4	Grade 3-4	Grade 1	Grade 2-4	Grade 3-4	Grade1	Grade 2-4	Grade 3-4

	Proportion of patients with elevated ALT											
	INFLECTRA® [2]						REMICADE®[3]					
RA	3 (1.0%)	0	0	123 (40.7%)	19 (6.3%)	5 (1.7%)	6 (2.0%)	0	0	133 (44.3%)	13 (4.3%)	4 (1.3%)
AS	1 (0.8%)	0	0	62 (48.4%)	12 (9.4%)	2 (1.6%)	5 (4.1%)	0	0	59 (48.4%)	12 (9.8%)	3 (2.5%)

[1]: CTCAE (Common Terminology Criteria for Adverse Events) grading will be applied to the lowest and highest post-baseline values (which will include all data from scheduled, unscheduled, and repeat visits) for all numeric parameters where possible according CTCAE version 4.
[2]: Total patient number in RA = 302, Total patient number in AS = 128
[3]: Total patient number in RA = 300, Total patient number in AS = 122

Table 20: Proportion of Patients with Elevated AST in INFLECTRA® Clinical Trials

	Proportion of patients with elevated AST											
	INFLECTRA® [2]						REMICADE®[3]					
	Lowest results[1]			Highest results[1]			Lowest results[1]			Highest results[1]		
	Grade 1	Grade 2-4	Grade 3-4	Grade 1	Grade 2-4	Grade 3-4	Grade 1	Grade 2-4	Grade 3-4	Grade 1	Grade 2-4	Grade 3-4
RA	2 (0.7%)	0	0	83 (27.5%)	6 (2.0%)	3 (1.0%)	5 (1.7%)	0	0	84 (28.0%)	7 (2.3%)	1 (0.3%)
AS	0	0	0	44 (34.4%)	6 (4.7%)	2 (1.6%)	1 (0.8%)	0	0	37 (30.3%)	3 (2.5%)	2 (1.6%)

[1]: CTCAE (Common Terminology Criteria for Adverse Events) grading will be applied to the lowest and highest post-baseline values (which will include all data from scheduled, unscheduled, and repeat visits) for all numeric parameters where possible according CTCAE version 4.
[2]: Total patient number in RA=302, Total patient number in AS=128
[3]: Total patient number in RA=300, Total patient number in AS=122

The difference in rates of ALT and AST elevations between INFLECTRA® and REMICADE® treatment groups are seen in Table 19 and Table 20.

DOSAGE AND ADMINISTRATION

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

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

For adult and paediatric patients, administer the infusion solution over a period of not less than 2 hours.

All patients administered INFLECTRA® are to be observed for at least one to two hours post infusion for side effects. Medications, an artificial airway and other appropriate materials must be available for the treatment of these effects (see PRECAUTIONS).

Shortened Infusions Across Adult Indications

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

Rheumatoid Arthritis in adults
Patients not previously treated with INFLECTRA®*:* Initially 3 mg/kg intravenous infusion over a 2-hour period is to be followed with additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

INFLECTRA® should be given in combination with methotrexate.

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

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. If a patient has an inadequate response or loses response after this period, the dose may be adjusted as described above. If adequate response is achieved, patients should be continued on the selected dose or dose frequency. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment or after dose adjustment.

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

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

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

Crohn's Disease
Moderate to severe Crohn's disease in adults and in children and adolescents (6 to 17 years)
For optimal long-term symptom control, 5 mg/kg given as a single intravenous infusion over a 2-hour period as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter. For patients who have an incomplete response during maintenance treatment, consideration may be given to adjusting the dose up to 10 mg/kg.

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

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

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

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

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

Ulcerative colitis in adults and in children and adolescents (6 to 17 years)
5 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion dose at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

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

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

Readministration for Crohn's disease, refractory fistulising Crohn's disease and Rheumatoid Arthritis
Readministration of a liquid formulation of infliximab, which is no longer in use, with a drug-free interval of 2 to 4 years following a previous infusion has been associated with a delayed hypersensitivity reaction in 10 patients with Crohn's disease (see PRECAUTIONS; ADVERSE EFFECTS). After a drug free interval of 16 weeks to 2 years, the risk of delayed hypersensitivity following readministration is not known. Therefore, after a drug free interval of 16 weeks, readministration is not recommended.

Readministration for Ankylosing Spondylitis
Data supporting readministration, other than every 6 weeks, are not available at this time (see PRECAUTIONS and ADVERSE EFFECTS).

Readministration for Psoriatic Arthritis
Data supporting readministration, other than every 8 weeks, are not available at this time (see PRECAUTIONS and ADVERSE EFFECTS).

Readministration for Psoriasis
Experience from intermittent treatment with infliximab in psoriasis after a period of no treatment suggests reduced efficacy and a higher incidence of infusion reactions when compared to the approved dosing guidance (see PRECAUTIONS and ADVERSE EFFECTS).

Readministration for ulcerative colitis
Data supporting readministration, other than every 8 weeks, are not available at this time (see PRECAUTIONS and ADVERSE EFFECTS).

Preparation and Administration
1. No physical biochemical compatibility studies have been conducted to evaluate the coadministration of INFLECTRA® with other agents. INFLECTRA® should not be infused concomitantly in the same intravenous line with other agents.

2. Calculate the dose and the required number of INFLECTRA® vials. Under aseptic conditions reconstitute each vial with 10 mL of preservative-free sterile Water for Injections, using a syringe equipped with a 21-gauge or smaller needle. Upon reconstitution, each mL of reconstituted solution contains 10 mg of infliximab. Remove flip-top from the vial and wipe the top with a 70% alcohol swab. Insert the syringe into the vial through the centre of the rubber stopper and direct the stream of sterile Water for Injections to the glass wall of the vial. Foaming during reconstitution is not unusual. Avoid prolonged or vigorous agitation. DO NOT SHAKE THE VIAL. Swirl gently until the lyophilised cake is completely dissolved. Allow the reconstituted solution to stand for 5 minutes. Because INFLECTRA® is a protein, the solution may develop a few fine translucent particles that do not affect its potency. The solution should be colourless to light yellow and opalescent. After reconstitution, the vials should be used immediately.

3. Further dilute the INFLECTRA® dose to a final volume of 250 mL with 0.9% sodium chloride solution for infusion, in either a 250 mL glass infusion bottle or infusion bag. Withdraw and discard a volume of 0.9% sodium chloride solution for infusion equal to the volume of the reconstituted INFLECTRA® dose; then, slowly add the INFLECTRA® to the bottle or bag of infusion solution. Gently mix. Depending on the number of INFLECTRA® vials used, the final concentration may range from 0.4 mg/mL to 4 mg/mL.

4. The solution for infusion must be administered over a period of not less than the infusion time recommended for the specific indication. Use only an infusion set with an in-line, sterile, nonpyrogenic, low protein-binding filter (pore size 1.2 μm or less).

5. INFLECTRA® infusion solution diluted in 0.9% sodium chloride is biochemically stable for 24 hours when stored between 2°C and 30°C. However, since no preservative is present, it is recommended the infusion begin within 3 hours after preparation and the solution not be stored for reuse. To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary hold at 2 to 8°C for no more than 24 hours. This product is for single use only and any unused portion of the solution should be discarded.

6. Parenteral drug products should be inspected visually for particulate matter or discolouration prior to administration. If opaque particles, discolouration or other foreign particulates are observed, the solution should not be used.

OVERDOSAGE
Single doses up to 20 mg/kg have been administered to patients without direct toxic effects. In case of overdosage, it is recommended that patients be monitored for any signs and symptoms of adverse reactions or effects, and appropriate symptomatic treatment be instituted immediately. Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS
INFLECTRA® 100 mg is supplied as a lyophilised powder in individually boxed single-use glass vials with rubber stoppers and aluminium crimps protected by plastic caps.
Store at 2º to 8º Celsius. Refrigerate do not freeze.

NAME AND ADDRESS OF THE SPONSOR
Pharmbio Pty Ltd
23 Blackwall Rd
Woy Woy
NSW 2256

POISON SCHEDULE
S4 - Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)
19 August 2015