1. NAME OF THE MEDICINAL PRODUCT

Remsima 100 mg I.V.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of infliximab. Infliximab is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology. After reconstitution each ml contains 10 mg of infliximab.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

The powder is white.

Patient safety information Card
The marketing of Remsima 100 mg I.V. is subject to a risk management plan (RMP), including a 'Patient safety information card'.
The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

Remsima 100 mg I.V. is a biosimilar medicinal product that has been demonstrated to be similar in quality, safety and efficacy to the reference medicinal product Remicade. Please be aware of any differences in the indications between the biosimilar medicinal product and the reference medicinal product. Information regarding biosimilar products can be found on the website of the Ministry of Health: https://www.gov.il/he/Departments/General/biosimilar

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Rheumatoid arthritis:
Remsima 100 mg I.V., in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

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

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

- Adult Crohn's disease:
Remsima 100 mg I.V. is indicated for:

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

- Paediatric Crohn's disease:
Remsima 100 mg I.V. is indicated for treatment of severe, active Crohn's disease in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy.

- Ulcerative colitis:
Remsima 100 mg I.V. is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

- Paediatric ulcerative colitis:
Remsima 100 mg I.V.is indicated for treatment of severely active ulcerative colitis in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

- Ankylosing spondylitis:
Remsima 100 mg I.V. is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

- Psoriatic arthritis:
Remsima 100 mg I.V. is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.
Remsima 100 mg I.V. should be administered:
- in combination with methotrexate
- or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.

Infliximab has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1).

- Psoriasis:
Remsima 100 mg I.V. is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen ultra-violet A (PUVA) (see section 5.1).

4.2 Posology and method of administration

Remsima 100 mg I.V. treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, inflammatory bowel diseases, ankylosing spondylitis, psoriatic arthritis or psoriasis. Remsima 100 mg I.V. should be administered intravenously. Remsima 100 mg I.V. infusions should be administered by qualified healthcare professionals trained to detect any infusion related issues. Patients treated with Remsima 100 mg I.V. should be given the package leaflet and the patient safety information card.

During Remsima 100 mg I.V. treatment, other concomitant therapies, e.g. corticosteroids and immunosuppressants should be optimised.

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous) is being administered to the patient, as prescribed. Remsima subcutaneous formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only.

Posology

Adults (≥18 years)

Rheumatoid arthritis

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

Remsima 100 mg I.V. must be given concomitantly with methotrexate.

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, consideration may be given to increase the dose step-wise by approximately 1.5 mg/kg, up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be considered. 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.

Moderately to severely active Crohn's disease
5 mg/kg given as an intravenous infusion followed by an additional 5 mg/kg infusion 2 weeks after the first infusion. If a patient does not respond after 2 doses, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 6 weeks of the initial infusion.

In responding patients, the alternative strategies for continued treatment are:
- Maintenance: Additional infusion of 5 mg/kg at 6 weeks after the initial dose, followed by infusions every 8 weeks or
- Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur (see 'Re-administration' below and section 4.4).

Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

Fistulising, active Crohn's disease
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion. If a patient does not respond after 3 doses, no additional treatment with infliximab should be given.

In responding patients, the alternative strategies for continued treatment are:
- Maintenance: Additional infusions of 5 mg/kg every 8 weeks or
- Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur followed by infusions of 5 mg/kg every 8 weeks (see 'Re-administration' below and section 4.4).

Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

In Crohn's disease, experience with re-administration if signs and symptoms of disease recur is limited and comparative data on the benefit/risk of the alternative strategies for continued treatment are lacking.

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

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

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

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

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

Re-administration for Crohn's disease and rheumatoid arthritis
If the signs and symptoms of disease recur, infliximab can be re-administered within 16 weeks following the last infusion. In clinical studies, delayed hypersensitivity reactions have been uncommon and have occurred after infliximab-free intervals of less than 1 year (see sections 4.4 and 4.8). The safety and efficacy of re-administration after an infliximab-free interval of more than 16 weeks has not been established. This applies to both Crohn's disease patients and rheumatoid arthritis patients.

Re-administration for ulcerative colitis
The safety and efficacy of re-administration, other than every 8 weeks, has not been established (see sections 4.4 and 4.8).
Re-administration for ankylosing spondylitis
The safety and efficacy of re-administration, other than every 6 to 8 weeks, has not been established (see sections 4.4 and 4.8).

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

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

Limited experience from re-treatment following disease flare by a re-induction regimen suggests a higher incidence of infusion reactions, including serious ones, when compared to 8-weekly maintenance treatment (see section 4.8).

Re-administration across indications
In case maintenance therapy is interrupted, and there is a need to restart treatment, use of a re-induction regimen is not recommended (see section 4.8). In this situation, infliximab should be re-initiated as a single dose followed by the maintenance dose recommendations described above.

Special populations

Elderly

Specific studies of infliximab in elderly patients have not been conducted. No major age-related differences in clearance or volume of distribution were observed in clinical studies. No dose adjustment is required (see section 5.2). For more information about the safety of infliximab in elderly patients (see sections 4.4 and 4.8).

Renal and/or hepatic impairment

Infliximab has not been studied in these patient populations. No dose recommendations can be made (see section 5.2).

Paediatric population

Crohn's disease (6 to 17 years)

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

Available data do not support further infliximab treatment in children and adolescents not responding within the first 10 weeks of treatment (see section 5.1).

Some patients may require a shorter dosing interval to maintain clinical benefit, while for others a longer dosing interval may be sufficient. Patients who have had their dose interval shortened to less than 8 weeks may be at greater risk for adverse reactions. Continued therapy with a shortened interval should be carefully considered in those patients who show no evidence of additional therapeutic benefit after a change in dosing interval.

The safety and efficacy of infliximab have not been studied in children with Crohn's disease below the age of 6 years. Currently available pharmacokinetic data are described in section 5.2 but no recommendation on a posology can be made in children younger than 6 years.

Ulcerative colitis (6 to 17 years)

5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in paediatric patients not responding within the first 8 weeks of treatment (see section 5.1).

The safety and efficacy of infliximab have not been studied in children with ulcerative colitis below the age of 6 years. Currently available pharmacokinetic data are described in section 5.2 but no recommendation on a posology can be made in children younger than 6 years.

Psoriasis

The safety and efficacy of infliximab in children and adolescents younger than 18 years for the indication of psoriasis have not been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis

The safety and efficacy of infliximab in children and adolescents younger than 18 years for the indications of juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis have not been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Juvenile rheumatoid arthritis

The safety and efficacy of infliximab in children and adolescents younger than 18 years for the indication of juvenile rheumatoid arthritis have not been established. Currently available data are described in sections 4.8 and 5.2 but no recommendation on a posology can be made.

Method of administration

Infliximab should be administered intravenously over a 2 hour period. All patients administered

infliximab are to be observed for at least 1-2 hours post-infusion for acute infusion-related reactions. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol and infusion rate may be slowed in order to decrease the risk of infusion-related reactions especially if infusion-related reactions have occurred previously (see section 4.4).

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, a slower infusion rate may be considered for future infusions if treatment is to be continued. Shortened infusions at doses >6 mg/kg have not been studied (see section 4.8).

For preparation and administration instructions, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to other murine proteins, or to any of the excipients listed in section 6.1.

Patients with tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections (see section 4.4).

Patients with moderate or severe heart failure (NYHA class III/IV) (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infusion reactions and hypersensitivity
Infliximab has been associated with acute infusion-related reactions, including anaphylactic shock, and delayed hypersensitivity reactions (see section 4.8).

Acute infusion reactions including anaphylactic reactions may develop during (within seconds) or within a few hours following infusion. If acute infusion reactions occur, the infusion must be interrupted immediately. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.
Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions. A low proportion of the infusion reactions was serious allergic reactions. An association between development of antibodies to infliximab and reduced duration of response has also been observed. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and a reduction in the frequency of infusion reactions. The effect of concomitant immunomodulator therapy was more profound in episodically treated patients than in patients given maintenance therapy. Patients who discontinue immunosuppressants prior to or during infliximab treatment are at greater risk of developing these antibodies. Antibodies to infliximab cannot always be detected in serum samples. If serious reactions occur, symptomatic treatment must be given and further infliximab infusions must not be administered (see section 4.8).

In clinical studies, delayed hypersensitivity reactions have been reported. Available data suggest an increased risk for delayed hypersensitivity with increasing infliximab-free interval. Patients should

be advised to seek immediate medical advice if they experience any delayed adverse reaction (see section 4.8). If patients are re-treated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.

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

Caution should be exercised when considering the use of infliximab in patients with chronic infection or a history of recurrent infections, including concomitant immunosuppressive therapy. Patients should be advised of and avoid exposure to potential risk factors for infection as appropriate.

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

It should be noted that suppression of TNF_α may mask symptoms of infection such as fever. Early recognition of atypical clinical presentations of serious infections and of typical clinical presentation of rare and unusual infections is critical in order to minimise delays in diagnosis and treatment.

Patients taking TNF-blockers are more susceptible to serious infections.
Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections have been observed in patients treated with infliximab. Some of these infections have been fatal; the most frequently reported opportunistic infections with a mortality rate of > 5% include pneumocystosis, candidiasis, listeriosis and aspergillosis.
Patients who develop a new infection while undergoing treatment with infliximab, should be monitored closely and undergo a complete diagnostic evaluation. Administration of infliximab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

Tuberculosis
There have been reports of active tuberculosis in patients receiving infliximab. It should be noted that in the majority of these reports tuberculosis was extrapulmonary, presenting as either local or disseminated disease.

Before starting treatment with infliximab, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, (e.g. tuberculin skin test, chest X-ray, and/or Interferon Gamma Release Assay), should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the patient's safety information card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

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

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below, the benefit/risk balance of infliximab therapy should be very carefully considered.

If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with antituberculosis therapy before the initiation of infliximab, and in accordance with local

recommendations.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, antituberculosis therapy should be considered before the initiation of infliximab.

Use of antituberculosis 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.
Some cases of active tuberculosis have been reported in patients treated with infliximab during and after treatment for latent tuberculosis.
All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g. persistent cough, wasting/weight loss, low-grade fever) appear during or after infliximab treatment.

Invasive fungal infections
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, and a physician with expertise in the diagnosis and treatment of invasive fungal infections should be consulted at an early stage when investigating these patients. Invasive fungal infections may present as disseminated rather than localised 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 taking into account both the risk for severe fungal infection and the risks of antifungal therapy.

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 of infliximab therapy.

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

Hepatitis B (HBV) reactivation
Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including infliximab, who are chronic carriers of this virus. Some cases have had fatal outcome.

Patients should be tested for HBV infection before initiating treatment with infliximab. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Carriers of HBV who require treatment with infliximab should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of treating patients who are carriers of HBV with antiviral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, infliximab should be stopped and effective antiviral therapy with appropriate supportive treatment should be initiated.

Hepatobiliary events
Cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of infliximab. Isolated cases of liver failure resulting in liver transplantation or death have occurred. 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 develop(s), infliximab should be discontinued, and a thorough investigation of the abnormality should be undertaken.

Concurrent administration of TNF-alpha inhibitor and anakinra
Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and

another TNFα-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse reactions seen with combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNFα-blocking agents. Therefore, the combination of infliximab and anakinra is not recommended.

Concurrent administration of TNF-alpha inhibitor and abatacept
In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of infliximab and abatacept is not recommended.

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

Switching between biological DMARDS
Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse reactions, including infection.

Vaccinations
It is recommended that patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating Remsima 100 mg I.V. therapy. Patients on infliximab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6).

In a subset of 90 adult patients with rheumatoid arthritis from the ASPIRE study a similar proportion of patients in each treatment group (methotrexate plus: placebo [n = 17], 3 mg/kg [n = 27] or 6 mg/kg infliximab [n = 46]) 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. However, studies from the published literature in various indications (e.g. rheumatoid arthritis, psoriasis, Crohn's disease) suggest that non-live vaccinations received during treatment with anti-TNF therapies, including infliximab, may elicit a lower immune response than in patients not receiving anti-TNF therapy.

Live vaccines/therapeutic infectious agents
In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines can result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with Remsima 100 mg I.V. is not recommended.

Infant exposure *in utero*
In infants exposed in utero to infliximab, fatal outcome due to disseminated Bacillus Calmette-Guérin (BCG) infection has been reported following administration of BCG vaccine after birth. A twelve month waiting period following birth is recommended before the administration of BCG live vaccine to infants exposed in utero to infliximab. A six month waiting period following birth is recommended before the administration of all other live vaccines to infants exposed *in utero* to infliximab.

Therapeutic infectious agents
Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with Remsima 100 mg I.V.

Autoimmune processes

The relative deficiency of TNFα caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Remsima 100 mg I.V. and is positive for antibodies against double-stranded DNA, further treatment with Remsima 100 mg I.V. must not be given (see section 4.8).

Neurological events

Use of TNF-blocking agents, including infliximab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of Remsima 100 mg I.V. therapy. Discontinuation of Remsima 100 mg I.V. should be considered if these disorders develop.

Malignancies and lymphoproliferative disorders

In the controlled portions of clinical studies of TNF-blocking agents, more cases of malignancies including lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During clinical studies of infliximab across all approved indications the incidence of lymphoma in infliximab-treated patients was higher than expected in the general population, but the occurrence of lymphoma was rare. In the post-marketing setting, cases of leukaemia have been reported in patients treated with a TNF-antagonist. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.

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

With the current knowledge, a risk for the development of lymphomas or other malignancies in patients treated with a TNF-blocking agent cannot be excluded (see section 4.8). 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.

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

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents (initiation of therapy ≤ 18 years of age), including infliximab in the post-marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in patients treated with TNF- blockers cannot be excluded.

Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) 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. Almost all patients had received treatment with AZA or 6-MP concomitantly with or immediately prior to a TNF-blocker. The vast majority of infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males. The potential risk with the combination of AZA or 6-MP and infliximab should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with infliximab cannot be excluded (see section 4.8).

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including infliximab (see section 4.8). Periodic skin examination is recommended,

particularly for patients with risk factors for skin cancer.

A population-based retrospective cohort study using data from Swedish national health registries found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age. Periodic screening should continue in women treated with Remsima 100 mg I.V., including those over 60 years of age.

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. Current data do not indicate that infliximab treatment influences the risk for developing dysplasia or colon cancer.

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 of continued therapy to the individual patients should be carefully considered by the clinician.

Heart failure
Remsima 100 mg I.V. should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and Remsima 100 mg I.V. must not be continued in patients who develop new or worsening symptoms of heart failure (see sections 4.3 and 4.8).

Haematologic reactions
There have been reports of pancytopenia, leucopenia, neutropenia, and thrombocytopenia in patients receiving TNF-blockers, including infliximab. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of Remsima 100 mg I.V. therapy should be considered in patients with confirmed significant haematologic abnormalities.

Others
The long half-life of infliximab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on infliximab should be closely monitored for infectious and non-infectious complications, and appropriate actions should be taken (see section 4.8).

Failure to respond to treatment for Crohn's disease may indicate the presence of a fixed fibrotic stricture that may require surgical treatment. There is no evidence to suggest that infliximab worsens or causes fibrotic strictures.

Special populations

Elderly
The incidence of serious infections in Remsima 100 mg I.V.-treated patients 65 years and older was greater than in those under 65 years of age. Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly (see section 4.8).

Paediatric population

Infections
In clinical studies, infections have been reported in a higher proportion of paediatric patients compared to adult patients (see section 4.8).

Vaccinations
It is recommended that paediatric patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating Remsima 100 mg I.V. therapy.

Paediatric patients on infliximab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6).

Malignancies and lymphoproliferative disorders
Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents (initiation of therapy ≤ 18 years of age), including infliximab in the post-marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-blockers cannot be excluded.

Post-marketing 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. Almost all patients had received treatment with AZA or 6-MP concomitantly with or immediately prior to a TNF-blocker. The vast majority of infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males. The potential risk with the combination of AZA or 6-MP and Remsima 100 mg I.V. should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with Remsima 100 mg I.V. cannot be excluded (see section 4.8).

Sodium content
Remsima 100 mg I.V. contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'. Remsima 100 mg I.V. is however, diluted in sodium chloride 9 mg/ml (0.9%) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet (see section 6.6).

Polysorbate 80 content
Remsima 100 mg I.V. contains 0.50 mg of polysorbate 80 (E433) in each dosage unit which is equivalent to 0.05 mg/ml. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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.

The combination of Remsima 100 mg I.V. with other biological therapeutics used to treat the same conditions as Remsima 100 mg I.V., including anakinra and abatacept, is not recommended (see section 4.4).

It is recommended that live vaccines not be given concurrently with Remsima 100 mg I.V.. It is also recommended that BCG live vaccine not be given to infants after *in utero* exposure to infliximab for 12 months following birth. A six month waiting period following birth is recommended before the administration of all other live vaccines to infants exposed in utero to infliximab.

It is recommended that therapeutic infectious agents not be given concurrently with Remsima 100 mg I.V. (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last Remsima 100 mg I.V. treatment.

Pregnancy
The moderate number of prospectively collected pregnancies exposed to infliximab resulting in live birth with known outcomes, including approximately 1100 exposed during the first trimester, does not indicate an increase in the rate of malformation in the newborn.

Based on an observational study from Northern Europe, an increased risk (OR, 95% CI; p-value) for C-section (1.50, 1.14-1.96; p=0.0032), preterm birth (1.48, 1.05-2.09; p=0.024), small for gestational age (2.79, 1.54-5.04; p=0.0007), and low birth weight (2.03, 1.41-2.94; p=0.0002) was observed in women exposed during pregnancy to infliximab (with or without immunomodulators/corticosteroids, 270 pregnancies) as compared to women exposed to immunomodulators and/or corticosteroids only (6,460 pregnancies). The potential contribution of exposure to infliximab and/or the severity of the underlying disease in these outcomes remains unclear.

Due to its inhibition of TNFα, infliximab administered during pregnancy could affect normal immune responses in the newborn. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, there was no indication of maternal toxicity, embryotoxicity or teratogenicity (see section 5.3).

The available clinical experience is limited. Infliximab should only be used during pregnancy if clearly needed.

Infliximab crosses the placenta and has been detected in the serum of infants up to 12 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including serious disseminated infection that can become fatal. Administration of BCG live vaccine to infants exposed to infliximab *in utero* is not recommended for 12 months after birth (see sections 4.4 and 4.5). Administration of all other live vaccines to infants exposed to infliximab *in utero* is not recommended for 6 months after birth. Cases of agranulocytosis have also been reported (see section 4.8).

Breast-feeding
Limited data from published literature indicate infliximab has been detected at low levels in human milk at concentrations up to 5% of the maternal serum level. Infliximab has also been detected in infant serum after exposure to infliximab via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, Remsima 100 mg I.V. could be considered for use during breast-feeding.

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

4.7 Effects on ability to drive and use machines

Remsima 100 mg I.V. may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of Remsima 100 mg I.V. (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
Upper respiratory tract infection was the most common adverse drug reaction (ADR) reported in

clinical trials, occurring in 25.3% of infliximab-treated patients compared with 16.5% of control patients. The most serious ADRs associated with the use of TNF blockers that have been reported for infliximab include HBV reactivation, CHF (congestive heart failure), serious infections (including sepsis, opportunistic infections and TB), serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, HSTCL, leukaemia, Merkel cell carcinoma, melanoma, paediatric malignancy, sarcoidosis/sarcoid-like reaction, intestinal or perianal abscess (in Crohn's disease), and serious infusion reactions (see section 4.4).

Tabulated list of adverse reactions

Table 1 lists ADRs based on experience from clinical studies as well as adverse reactions, some with fatal outcome, reported from post-marketing experience. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1
Undesirable effects in clinical studies and from post-marketing experience

Infections and infestations	
Very Common:	Viral infection (e.g. influenza, herpes virus infection).
Common:	Bacterial infections (e.g. sepsis, cellulitis, abscess).
Uncommon:	Tuberculosis, fungal infections (e.g. candidiasis, onychomycosis).
Rare:	Meningitis, opportunistic infections (such as invasive fungal infections [pneumocystosis, histoplasmosis, aspergillosis, coccidioidomycosis, cryptococcosis, blastomycosis], bacterial infections [atypical mycobacterial, listeriosis, salmonellosis], and viral infections [cytomegalovirus]), parasitic infections, hepatitis B reactivation.
Not known	Vaccine breakthrough infection (after *in utero* exposure to infliximab)*.
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare:	Lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia, melanoma, cervical cancer
Not known:	Hepatosplenic T-cell lymphoma (primarily in adolescents and young adult males with Crohn's disease or ulcerative colitis), Merkel cell carcinoma, Kaposi's sarcoma.
Blood and lymphatic system disorders	
Common:	Neutropenia, leucopenia, anaemia, lymphadenopathy.
Uncommon:	Thrombocytopenia, lymphopenia, lymphocytosis.
Rare:	Agranulocytosis (including infants exposed *in utero* to infliximab), thrombotic thrombocytopenic purpura, pancytopenia, haemolytic anaemia, idiopathic thrombocytopenic purpura.
Immune system disorders	
Common:	Allergic respiratory symptom.
Uncommon:	Anaphylactic reaction, lupus-like syndrome, serum sickness or serum sickness-like reaction.
Rare:	Anaphylactic shock, vasculitis, sarcoid-like reaction.

Metabolism and nutrition disorders		
	Uncommon:	Dyslipidaemia
Psychiatric disorders		
	Common:	Depression, insomnia.
	Uncommon:	Amnesia, agitation, confusion, somnolence, nervousness.
	Rare:	Apathy.
Nervous system disorders		
	Very common:	Headache.
	Common:	Vertigo, dizziness, hypoaesthesia, paraesthesia.
	Uncommon:	Seizure, neuropathy.
	Rare:	Transverse myelitis, central nervous system demyelinating disorders (multiple sclerosis-like disease and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy).
	Not known:	Cerebrovascular accidents in close temporal association with infusion.
Eye disorders		
	Common:	Conjunctivitis.
	Uncommon:	Keratitis, periorbital oedema, hordeolum.
	Rare:	Endophthalmitis.
	Not known	Transient visual loss occurring during or within 2 hours of infusion.
Cardiac disorders		
	Common:	Tachycardia, palpitation.
	Uncommon:	Cardiac failure (new onset or worsening), arrhythmia, syncope, bradycardia.
	Rare:	Cyanosis, pericardial effusion.
	Not known:	Myocardial ischaemia/myocardial infarction
Vascular disorders		
	Common:	Hypotension, hypertension, ecchymosis, hot flush, flushing.
	Uncommon:	Peripheral ischaemia, thrombophlebitis, haematoma.
	Rare:	Circulatory failure, petechia, vasospasm.
Respiratory, thoracic and mediastinal disorders		
	Very common:	Upper respiratory tract infection, sinusitis.
	Common:	Lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, epistaxis.
	Uncommon:	Pulmonary oedema, bronchospasm, pleurisy, pleural effusion.
	Rare:	Interstitial lung disease (including rapidly progressive disease, lung fibrosis and pneumonitis).
Gastrointestinal disorders		
	Very common:	Abdominal pain, nausea.
	Common:	Gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastroesophageal reflux, constipation.
	Uncommon:	Intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis.
Hepatobiliary disorders		
	Common:	Hepatic function abnormal, transaminases increased.
	Uncommon:	Hepatitis, hepatocellular damage, cholecystitis.
	Rare:	Autoimmune hepatitis, jaundice.
	Not known:	Liver failure.

Skin and subcutaneous tissue disorders	
Common:	New onset or worsening psoriasis including pustular psoriasis (primarily palm & soles), urticaria, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia.
Uncommon:	Bullous eruption, seborrhoea, rosacea, skin papilloma, hyperkeratosis, abnormal skin pigmentation.
Rare:	Toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, furunculosis, linear IgA bullous dermatosis (LABD), acute generalised exanthematous pustulosis (AGEP), lichenoid reactions.
Not known:	worsening of symptoms of dermatomyositis
Musculoskeletal and connective tissue disorders	
Common:	Arthralgia, myalgia, back pain.
Renal and urinary disorders	
Common:	Urinary tract infection.
Uncommon:	Pyelonephritis.
Reproductive system and breast disorders	
Uncommon:	Vaginitis.
General disorders and administration site conditions	
Very common:	Infusion-related reaction, pain.
Common:	Chest pain, fatigue, fever, injection site reaction, chills, oedema.
Uncommon:	Impaired healing.
Rare:	Granulomatous lesion.
Investigations	
Uncommon:	Autoantibody positive, weight increased[1].
Rare:	Complement factor abnormal.
Injury, poisoning, and procedural complications	
Not known:	Post-procedural complication (including infectious and non-infectious complications)

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

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

Description of selected adverse drug reactions

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 III clinical studies, 18% of infliximab-treated patients compared with 5% of placebo-treated patients experienced an infusion-related reaction. Overall, a higher proportion of patients receiving infliximab monotherapy experienced an infusion- related reaction compared to patients receiving infliximab with concomitant immunomodulators.
Approximately 3% of patients discontinued treatment due to infusion-related reactions and all patients recovered with or without medical therapy. Of infliximab-treated patients who had an infusion reaction during the induction period, through week 6, 27% experienced an infusion reaction during the maintenance period, week 7 through week 54. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance

period.
In a clinical study of patients with rheumatoid arthritis (ASPIRE), 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. In this trial, sixty six percent of the patients (686 out of 1,040) received at least one shortened infusion of 90 minutes or less and 44% of the patients (454 out of 1,040) 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 patients and serious infusion reactions occurred in 0.4% of patients.

In a clinical study of patients with Crohn's disease (SONIC), infusion-related reactions occurred in 16.6% (27/163) of patients receiving infliximab monotherapy, 5% (9/179) of patients receiving infliximab in combination with AZA, and 5.6% (9/161) of patients receiving AZA monotherapy. One serious infusion reaction (< 1%) occurred in a patient on infliximab monotherapy.

In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal oedema and severe bronchospasm, and seizure have been associated with infliximab administration (see section 4.4).
Cases of transient visual loss occurring during or within 2 hours of infliximab infusion have been reported. Events (some fatal) of myocardial ischaemia/infarction and arrhythmia have been reported, some in close temporal association with infusion of infliximab; cerebrovascular accidents have also been reported in close temporal association with infusion of infliximab.

Infusion reactions following re-administration of infliximab:

A clinical study in patients with moderate to severe psoriasis was designed to assess the efficacy and safety of long-term maintenance therapy versus re-treatment with an induction regimen of infliximab (maximum of four infusions at 0, 2, 6 and 14 weeks) following disease flare. Patients did not receive any concomitant immunosuppressant therapy. In the re-treatment arm, 4% (8/219) of patients experienced a serious infusion reaction versus < 1% (1/222) on maintenance therapy. The majority of serious infusion reactions occurred during the second infusion at week 2. The interval between the last maintenance dose and the first re-induction dose ranged from 35-231 days. Symptoms included, but were not limited to, dyspnea, urticaria, facial 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 clinical studies delayed hypersensitivity reactions have been uncommon and have occurred after infliximab-free intervals of less than 1 year. In the psoriasis studies, delayed hypersensitivity reactions occurred early in the treatment course. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients experiencing pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and headache.

There are insufficient data on the incidence of delayed hypersensitivity reactions after infliximab-free intervals of more than 1 year but limited data from clinical studies suggest an increased risk for delayed hypersensitivity with increasing infliximab-free interval (see section 4.4).

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

Immunogenicity:

Patients who developed antibodies to infliximab were more likely (approximately 2-3 fold) to develop infusion-related reactions. Use of concomitant immunosuppressant agents appeared to reduce the frequency of 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 14% of patients with any immunosuppressant therapy, and in 24% of patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, 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). In Crohn's disease patients who received maintenance treatment, antibodies to infliximab occurred overall in 3.3% of patients receiving immunosuppressants and in 13.3% of patients not receiving immunosuppressants. The antibody incidence was 2-3 fold higher for patients treated episodically. Due to methodological limitations, a negative assay did not exclude the presence of antibodies to infliximab. Some patients who developed high titres of antibodies to infliximab had evidence of reduced efficacy. In psoriasis patients treated with infliximab as a maintenance regimen in the absence of concomitant immunomodulators, approximately 28% developed antibodies to infliximab (see section 4.4: "Infusion reactions and hypersensitivity").

Infections:
Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections have been observed in patients receiving infliximab. Some of these infections have been fatal; the most frequently reported opportunistic infections with a mortality rate of > 5% include pneumocystosis, candidiasis, listeriosis and aspergillosis (see section 4.4).

In clinical studies 36% of infliximab-treated patients were treated for infections compared with 25% of placebo-treated patients.
In rheumatoid arthritis clinical studies, the incidence of serious infections including pneumonia was higher in infliximab plus methotrexate-treated patients compared with methotrexate alone especially at doses of 6 mg/kg or greater (see section 4.4).

In post-marketing spontaneous reporting, infections are the most common serious adverse reaction. Some of the cases have resulted in a fatal outcome. Nearly 50% of reported deaths have been associated with infection. Cases of tuberculosis, sometimes fatal, including miliary tuberculosis and tuberculosis with extra-pulmonary location have been reported (see section 4.4).

Malignancies and lymphoproliferative disorders:

In clinical studies with infliximab in which 5,780 patients were treated, representing 5,494 patient years, 5 cases of lymphomas and 26 non-lymphoma malignancies were detected as compared with no lymphomas and 1 non-lymphoma malignancy in 1,600 placebo-treated patients representing 941 patient years.

In long-term safety follow-up of clinical studies with infliximab of up to 5 years, representing 6,234 patients-years (3,210 patients), 5 cases of lymphoma and 38 cases of non-lymphoma malignancies were reported.

Cases of malignancies, including lymphoma, have also been reported in the post-marketing setting (see section 4.4).

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

A population-based retrospective cohort study found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age (see section 4.4).

In addition, post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with infliximab with the vast majority of cases occurring in Crohn's disease and ulcerative colitis, and most of whom were adolescent or young adult males (see section 4.4).

Heart failure:
In a Phase II study aimed at evaluating infliximab in CHF, higher incidence of mortality due to worsening of heart failure were seen in patients treated with infliximab, especially those treated with the higher dose of 10 mg/kg (i.e. twice the maximum approved dose). In this study 150 patients with NYHA Class III-IV CHF (left ventricular ejection fraction ≤ 35%) were treated with 3 infusions of infliximab 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 38 weeks, 9 of 101 patients treated with infliximab (2 at 5 mg/kg and 7 at 10 mg/kg) died compared to one death among the 49 patients on placebo.
There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. There have also been post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.

Hepatobiliary events:
In clinical studies, 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 Upper Limit of Normal (ULN) have been observed (see Table 2). 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 therapy. In post- marketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving infliximab (see section 4.4).

Table 2
Proportion of patients with increased ALT activity in clinical studies

Indication	Number of patients[3]		Median follow-up (wks)[4]		≥3 x ULN		≥5 x ULN	
	placebo	infliximab	placebo	infliximab	placebo	infliximab	placebo	infliximab
Rheumatoid arthritis[1]	375	1,087	58.1	58.3	3.2%	3.9%	0.8%	0.9%
Crohn's disease[2]	324	1,034	53.7	54.0	2.2%	4.9%	0.0%	1.5%
Paediatric Crohn's disease	N/A	139	N/A	53.0	N/A	4.4%	N/A	1.5%
Ulcerative colitis	242	482	30.1	30.8	1.2%	2.5%	0.4%	0.6%
Paediatric Ulcerative colitis	N/A	60	N/A	49.4	N/A	6.7%	N/A	1.7%
Ankylosing spondylitis	76	275	24.1	101.9	0.0%	9.5%	0.0%	3.6%
Psoriatic arthritis	98	191	18.1	39.1	0.0%	6.8%	0.0%	2.1%
Plaque psoriasis	281	1,175	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 studies in Crohn's disease, ACCENT I and ACCENT II, received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in the ALT analysis. In the Phase IIIb trial in Crohn's disease, SONIC, placebo patients received AZA 2.5 mg/kg/day as active control in addition to placebo infliximab infusions.
[3] Number of patients evaluated for ALT.
[4] Median follow-up is based on patients treated.

Antinuclear antibodies (ANA)/Anti-double-stranded DNA (dsDNA) antibodies:
Approximately half of infliximab-treated patients in clinical studies who were ANA negative at baseline developed a positive ANA during the study compared with approximately one fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately 17% of infliximab-treated patients compared with 0% of placebo-treated patients. At the last evaluation, 57% of infliximab-treated patients remained anti-dsDNA positive. Reports of lupus and lupus-like syndromes, however, remain uncommon (see section 4.4).

Paediatric population

Juvenile rheumatoid arthritis patients:
Infliximab was studied in a clinical study in 120 patients (age range: 4-17 years old) with active juvenile rheumatoid arthritis despite methotrexate. Patients received 3 or 6 mg/kg infliximab as a 3-dose induction regimen (weeks 0, 2, 6 or weeks 14, 16, 20, respectively) followed by maintenance therapy every 8 weeks, in combination with methotrexate.

Infusion reactions
Infusion reactions occurred in 35% of patients with juvenile rheumatoid arthritis 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 (see section 4.4).

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 (see section 4.4).

Paediatric Crohn's disease patients:
The following adverse reactions were reported more commonly in paediatric Crohn's disease patients in the REACH study (see section 5.1) than in adult Crohn's disease patients: anaemia (10.7%), blood in stool (9.7%), leucopenia (8.7%), flushing (8.7%), viral infection (7.8%), neutropenia (6.8%), bacterial infection (5.8%), and respiratory tract allergic reaction (5.8%). In addition, bone fracture (6.8%) was reported, however, a causal association has not been established. Other special considerations are discussed below.

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

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

Infections
In the REACH study, infections were reported in 56.3% of randomised subjects treated with infliximab. Infections were reported more frequently for subjects who received q8 week as opposed to q12 week infusions (73.6% and 38.0%, respectively), while serious infections were reported for 3 subjects in the q8 week and 4 subjects in the q12 week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Three cases of pneumonia (1 serious) and 2 cases of herpes zoster (both non-serious) were reported.

Paediatric ulcerative colitis patients:
Overall, the adverse reactions reported in the paediatric ulcerative colitis trial (C0168T72) and adult ulcerative colitis (ACT 1 and ACT 2) studies were generally consistent. In C0168T72, the most common adverse reactions were upper respiratory tract infection, pharyngitis, abdominal pain, fever, and headache. The most common adverse event was worsening of ulcerative colitis, the incidence of which was higher in patients on the q12 week vs. the q8 week dosing regimen.

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 q8 week and 3 of 23 (13.0%) in the q12 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.

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). The overall incidence of infections in C0168T72 was 13/22 (59%) in the every 8 week maintenance treatment group and 14/23 (60.9%) in the every 12 week maintenance treatment group. Upper respiratory tract infection (7/60 [12%]) and pharyngitis (5/60 [8%]) were the most frequently reported respiratory system infections. Serious infections were reported in 12% (7/60) of all treated patients.

In this study, there were more patients in the 12 to 17 year age group than in the 6 to 11 year age group (45/60 [75.0%]) vs.15/60 [25.0%]). While the numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on safety events, there were higher proportions of patients with serious adverse events and discontinuation due to adverse events in the younger age group than in the older age group. While the proportion of patients with infections was also higher in the younger age group, for serious infections, the proportions were similar in the two age groups.
Overall proportions of adverse events and infusion reactions were similar between the 6 to 11 and 12 to 17 year age groups.

Post-marketing experience:
Post-marketing spontaneous serious adverse reactions with infliximab in the paediatric population have included malignancies including hepatosplenic T-cell lymphomas, transient hepatic enzyme abnormalities, lupus-like syndromes, and positive auto-antibodies (see sections 4.4 and 4.8).

Additional information on special populations

Elderly
In rheumatoid arthritis clinical studies, the incidence of serious infections was greater in infliximab plus methotrexate-treated patients 65 years and older (11.3%) than in those under 65 years of age (4.6%). In patients treated with methotrexate alone, the incidence of serious infections was 5.2% in patients 65 years and older compared to 2.7% in patients under 65 (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il
In addition, you can report to Padagis via the following address: Padagis.co.il

4.9 Overdose

No case of overdose has been reported. Single doses up to 20 mg/kg have been administered without toxic effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, tumour necrosis factor alpha (TNF_α) inhibitors, ATC code: L04AB02.

Mechanism of action
Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF_α but not to lymphotoxin α ($TNF_ß$).

Pharmacodynamic effects
Infliximab inhibits the functional activity of TNF_α in a wide variety of *in vitro* bioassays. Infliximab prevented disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNF_α and when administered after disease onset, it allowed eroded joints to heal. *In vivo*, infliximab rapidly forms stable complexes with human TNF_α, a process that parallels the loss of TNF_α bioactivity.

Elevated concentrations of TNFα have been found in the joints of rheumatoid arthritis patients and correlate with elevated disease activity. In 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 infliximab treatment, patients exhibited decreased levels of serum interleukin 6 (IL-6) and C-reactive protein (CRP)**,** and increased haemoglobin levels in rheumatoid arthritis patients with reduced haemoglobin levels, compared with baseline. Peripheral blood lymphocytes further showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared with untreated patients' cells. In psoriasis patients, treatment with infliximab resulted in decreases in epidermal inflammation and normalisation of keratinocyte differentiation in psoriatic plaques. In psoriatic arthritis, short term treatment with infliximab reduced the number of T-cells and blood vessels in the synovium and psoriatic skin.

Histological evaluation of colonic biopsies, obtained before and 4 weeks after administration of infliximab, revealed a substantial reduction in detectable TNFα. Infliximab treatment of Crohn's disease patients was also associated with a substantial reduction of the commonly elevated serum inflammatory marker, CRP. Total peripheral white blood cell counts were minimally affected in infliximab-treated patients, although changes in lymphocytes, monocytes and neutrophils reflected shifts towards normal ranges. Peripheral blood mononuclear cells (PBMC) from infliximab-treated patients showed undiminished proliferative responsiveness to stimuli compared with untreated patients, and no substantial changes in cytokine production by stimulated PBMC were observed following treatment with infliximab. Analysis of lamina propria mononuclear cells obtained by biopsy of the intestinal mucosa showed that infliximab treatment caused a reduction in the number of cells capable of expressing TNFα and interferonγ. Additional histological studies provided evidence that treatment with infliximab reduces the infiltration of inflammatory cells into affected areas of the intestine and the presence of inflammation markers at these sites. Endoscopic studies of intestinal mucosa have shown evidence of mucosal healing in infliximab-treated patients.

Clinical efficacy and safety

Adult rheumatoid arthritis

The efficacy of infliximab was assessed in two multicentre, randomised, double-blind, pivotal clinical studies: ATTRACT and ASPIRE. In both studies concurrent use of stable doses of folic acid, oral corticosteroids (≤ 10 mg/day) and/or non-steroidal antiinflammatory drugs (NSAIDs) was permitted.

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

The ATTRACT study evaluated responses at 30, 54 and 102 weeks in a placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with methotrexate. Approximately 50% of patients were in functional Class III. Patients received placebo, 3 mg/kg or 10 mg/kg infliximab at weeks 0, 2 and 6, and then every 4 or 8 weeks thereafter. All patients were on stable methotrexate doses (median 15 mg/wk) 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 3. Higher degrees of clinical response (ACR50 and ACR70) were observed in all infliximab groups at 30 and 54 weeks compared with methotrexate alone.

A reduction in the rate of the progression of structural joint damage (erosions and joint space narrowing) was observed in all infliximab groups at 54 weeks (Table 3).

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 3
Effects on ACR20, Structural Joint Damage and Physical Function at week 54, ATTRACT

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

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

The ASPIRE study evaluated responses at 54 weeks in 1,004 methotrexate naive patients with early (≤ 3 years disease duration, median 0.6 years) active rheumatoid arthritis (median swollen and tender joint count of 19 and 31, respectively). All patients received methotrexate (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 4.

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 4
Effects on ACRn, Structural Joint Damage and Physical Function at week 54, ASPIRE

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

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

Data to support dose titration in rheumatoid arthritis come from ATTRACT, ASPIRE and the START study. START was a randomised, multicentre, double-blind, 3-arm, parallel-group safety study. In one of the study arms (group 2, n=329), patients with an inadequate response were allowed to dose titrate with 1.5 mg/kg increments from 3 up to 9 mg/kg. The majority (67%) of these patients did not require any dose titration. Of the patients who required a dose titration, 80% achieved clinical response and the majority (64%) of these required only one adjustment of 1.5 mg/kg.

Adult Crohn's disease

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

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

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

Maintenance treatment in moderately to severely active Crohn's disease in adults
The efficacy of repeated infusions with infliximab was studied in a 1-year clinical study (ACCENT I). A total of 573 patients with moderately to severely active Crohn's disease (CDAI ≥ 220 ≤ 400)

received a single infusion of 5 mg/kg at week 0. 178 of the 580 enrolled patients (30.7%) were defined as having severe disease (CDAI score > 300 and concomitant corticosteroid and/or immunosuppressants) corresponding to the population defined in the indication (see section 4.1). At week 2, all patients were assessed for clinical response and randomised to one of 3 treatment groups; a placebo maintenance group, 5 mg/kg maintenance group and 10 mg/kg maintenance group. All 3 groups received repeated infusions at week 2, 6 and every 8 weeks thereafter.

Of the 573 patients randomised, 335 (58%) achieved clinical response by week 2. These patients were classified as week-2 responders and were included in the primary analysis (see Table 5). Among patients classified as non-responders at week 2, 32% (26/81) in the placebo maintenance group and 42% (68/163) in the infliximab group achieved clinical response by week 6. There was no difference between groups in the number of late responders thereafter.

The co-primary endpoints were the proportion of patients in clinical remission (CDAI<150) at week 30 and time to loss of response through week 54. Corticosteroid tapering was permitted after week 6.

Table 5
Effects on response and remission rate, data from ACCENT I (Week-2 responders)

	ACCENT I (week-2 responders) % of Patients		
	Placebo Maintenance (n=110)	Infliximab Maintenance 5 mg/kg (n=113) (p value)	Infliximab Maintenance 10 mg/kg (n=112) (p value)
Median time to loss of response through week 54	19 weeks	38 weeks (0.002)	>54 weeks (<0.001)
Week 30			
Clinical Response[a]	27.3	51.3 (<0.001)	59.1 (<0.001)
Clinical Remission	20.9	38.9 (0.003)	45.5 (<0.001)
Steroid-Free Remission	10.7 (6/56)	31.0 (18/58) (0.008)	36.8 (21/57) (0.001)
Week 54			
Clinical Response[a]	15.5	38.1 (<0.001)	47.7 (<0.001)
Clinical Remission	13.6	28.3 (0.007)	38.4 (<0.001)
Sustained Steroid-Free Remission[b]	5.7 (3/53)	17.9 (10/56) (0.075)	28.6 (16/56) (0.002)

a: Reduction in CDAI ≥25% and ≥70 points.
b: CDAI<150 at both week 30 and 54 and not receiving corticosteroids in the 3 months prior to week 54 among patients who were receiving corticosteroids at baseline.

Beginning at week 14, patients who had responded to treatment, but subsequently lost their clinical benefit, were allowed to cross over to a dose of infliximab 5 mg/kg higher than the dose to which they were originally randomised. Eighty-nine percent (50/56) of patients who lost clinical response on infliximab 5 mg/kg maintenance therapy after week 14 responded to treatment with infliximab 10 mg/kg.

Improvements in quality of life measures, a reduction in disease-related hospitalisations and

corticosteroid use were seen in the infliximab maintenance groups compared with the placebo maintenance group at weeks 30 and 54.

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

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

Table 6
Percent of patients achieving corticosteroid-free clinical remission at Week 26, SONIC

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

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

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

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

Concurrent use of stable doses of conventional therapies was permitted, and 83% of patients continued to receive at least one of these therapies. Patients received three doses of either placebo or infliximab at weeks 0, 2 and 6. Patients were followed up to 26 weeks. The primary endpoint was the proportion of patients who experienced a clinical response, defined as ≥ 50% reduction from baseline in the number of fistulae draining upon gentle compression on at least two consecutive visits (4 weeks apart), without an increase in the use of medicinal products 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 fistulae was achieved in 55% of infliximab-treated patients compared with 13% of placebo-treated patients (p = 0.001).

Maintenance treatment in fistulising active Crohn's disease
The efficacy of repeated infusions with infliximab in patients with fistulising Crohn's disease was

studied in a 1-year clinical study (ACCENT II). A total of 306 patients received 3 doses of infliximab 5 mg/kg at week 0, 2 and 6. At baseline, 87% of the patients had perianal fistulae, 14% had abdominal fistulae, 9% had rectovaginal fistulae. The median CDAI score was 180. At week 14, 282 patients were assessed for clinical response and randomised to receive either placebo or 5 mg/kg infliximab every 8 weeks through week 46.

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

Table 7
Effects on response rate, data from ACCENT II (Week-14 responders)

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

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

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

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

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

Adult 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.

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

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg	Combined
Subjects randomised	244	242	242	484
Percentage of subjects in clinical response and in sustained clinical response				
Clinical response at week 8[a]	33.2%	66.9%	65.3%	66.1%
Clinical response at week 30[a]	27.9%	49.6%	55.4%	52.5%
Sustained response (clinical response at both week 8 and week 30)[a]	19.3%	45.0%	49.6%	47.3%
Percentage of subjects in clinical remission and sustained remission				
Clinical remission at week 8[a]	10.2%	36.4%	29.8%	33.1%
Clinical remission at week 30[a]	13.1%	29.8%	36.4%	33.1%
Sustained remission (in remission at both week 8 and week 30)[a]	5.3%	19.0%	24.4%	21.7%
Percentage of subjects with mucosal healing				
Mucosal healing at week 8[a]	32.4%	61.2%	60.3%	60.7%
Mucosal healing at week 30[a]	27.5%	48.3%	52.9%	50.6%

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

The efficacy of infliximab through week 54 was assessed in the ACT 1 study.
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%, $p < 0.001$, pooled ACT 1 & ACT 2 data) and week 54 (21.0% vs. 8.9%, $p=0.022$, ACT1 data).

The pooled data analysis from the ACT 1 and ACT 2 studies and their extensions, analysed from baseline through 54 weeks, demonstrated a reduction of ulcerative colitis-related hospitalisations and surgical procedures with infliximab treatment. The number of ulcerative colitis-related hospitalisations was significantly lower in the 5 and 10 mg/kg infliximab treatment groups than in the placebo group (mean number of hospitalisations per 100 subject-years: 21 and 19 vs. 40 in the placebo group; $p=0.019$ and $p=0.007$, respectively). The number of ulcerative colitis-related surgical procedures was also lower in the 5 and 10 mg/kg infliximab treatment groups than in the placebo group (mean number of surgical procedures per 100 subject-years: 22 and 19 vs. 34; $p=0.145$ and $p=0.022$, respectively).

The proportion of subjects who underwent colectomy at any time within 54 weeks following the first infusion of study agent were collected and pooled from the ACT 1 and ACT 2 studies and their extensions. Fewer subjects underwent colectomy in the 5 mg/kg infliximab group (28/242 or 11.6% [N.S.]) and the 10 mg/kg infliximab group (18/242 or 7.4% [$p=0.011$]) than in the placebo group (36/244; 14.8%).

The reduction in incidence of colectomy was also examined in another randomised, double-blind study (C0168Y06) in hospitalised patients (n=45) with moderately to severely active ulcerative colitis who failed to respond to intravenous corticosteroids and who were therefore at higher risk for colectomy.
Significantly fewer colectomies occurred within 3 months of study infusion in patients who received a single dose of 5 mg/kg infliximab compared to patients who received placebo (29.2% vs. 66.7% respectively, p=0.017).

In ACT 1 and ACT 2, infliximab improved quality of life, confirmed by statistically significant improvement in both a disease specific measure, IBDQ, and by improvement in the generic 36-item short form survey SF-36.

Adult 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).

In the first study (P01522), which had a 3 month double-blind phase, 70 patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6 (35 patients in each group). At week 12, placebo patients were switched to infliximab 5 mg/kg 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.

In the second clinical study (ASSERT), 279 patients were randomised to receive either placebo (Group 1, n=78) or 5 mg/kg infliximab (Group 2, n=201) at 0, 2 and 6 weeks and every 6 weeks to week 24. Thereafter, all subjects continued on infliximab every 6 weeks to week 96. Group 1 received 5 mg/kg infliximab. In group 2, starting with the week 36 infusion, patients who had a BASDAI ≥ 3 at 2 consecutive visits, received 7.5 mg/kg infliximab every 6 weeks thereafter through week 96.

In ASSERT, improvement in signs and symptoms was observed as early as week 2. At week 24, the number of ASAS 20 responders was 15/78 (19%) in the placebo group, and 123/201 (61%) in the 5 mg/kg infliximab group ($p < 0.001$). There were 95 subjects from group 2 who continued on 5 mg/kg every 6 weeks. At 102 weeks there were 80 subjects still on infliximab treatment and among those, 71 (89%) were ASAS 20 responders.

In P01522, improvement in signs and symptoms was also observed as early as week 2. At week 12, the number of BASDAI 50 responders were 3/35 (9%) in the placebo group, and 20/35 (57%) in the 5 mg/kg group ($p < 0.01$). There were 53 subjects who continued on 5 mg/kg every 6 weeks. At 102 weeks there were 49 subjects still on infliximab treatment and among those, 30 (61%) were BASDAI 50 responders.

In both studies, physical function and quality of life as measured by the BASFI and the physical component score of the SF-36 were also improved significantly.

Adult psoriatic arthritis

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

In the first clinical study (IMPACT), efficacy and safety of infliximab were studied in 104 patients with active polyarticular psoriatic arthritis. 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 clinical study (IMPACT 2), efficacy and safety of infliximab were studied in 200 patients with active psoriatic arthritis (≥ 5 swollen joints and ≥ 5 tender joints). Forty six percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6, 14, and 22 (100 patients in each group). At week 16, 47 placebo patients with < 10% improvement from baseline in both swollen and tender joint counts were switched to infliximab induction (early escape). At week 24, all placebo-treated patients crossed over to infliximab induction. Dosing continued for all patients through week 46.

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

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

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

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

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

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

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

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

Radiographic changes were assessed in IMPACT 2. Radiographs of hands and feet were collected at baseline, weeks 24 and 54. Infliximab treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment at the week 24 primary endpoint as measured by change from baseline in total modified vdH-S score (mean ± SD score was 0.82 ± 2.62 in the placebo group compared with -0.70 ± 2.53 in the infliximab group; $p < 0.001$). In the infliximab group, the mean change in total modified vdH-S score remained below 0 at the week 54 timepoint.

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

Adult 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.

SPIRIT evaluated the efficacy of infliximab induction therapy in 249 patients with plaque psoriasis that had previously received PUVA or systemic therapy. Patients received either 3 or 5 mg/kg infliximab or placebo infusions at weeks 0, 2 and 6. Patients with a PGA score ≥3 were eligible to receive an additional infusion of the same treatment at week 26.
In SPIRIT, the proportion of patients achieving PASI 75 at week 10 was 71.7% in the 3 mg/kg infliximab group, 87.9% in the 5 mg/kg infliximab group, and 5.9% in the placebo group ($p < 0.001$). By week 26, twenty weeks after the last induction dose, 30% of patients in the 5mg/kg group and 13.8% of patients in the 3mg/kg group were PASI 75 responders. Between weeks 6 and 26, symptoms of psoriasis gradually returned with a median time to disease relapse of > 20 weeks. No rebound was observed.
EXPRESS evaluated the efficacy of infliximab induction and maintenance therapy in 378 patients with plaque psoriasis. Patients received 5 mg/kg infliximab- or placebo-infusions at weeks 0, 2 and 6 followed by maintenance therapy every 8 weeks through week 22 in the placebo group and through week 46 in the infliximab group. At week 24, the placebo group crossed over to infliximab induction therapy (5 mg/kg) followed by infliximab maintenance therapy (5 mg/kg). Nail psoriasis was assessed using the Nail Psoriasis Severity Index (NAPSI). Prior therapy with PUVA, methotrexate, ciclosporin, or acitretin had been received by 71.4% of patients, although they were not necessarily therapy resistant. Key results are presented in Table 10. In infliximab treated subjects, significant PASI 50 responses were apparent at the first visit (week 2) and PASI 75 responses by the second visit (week 6). Efficacy was similar in the subgroup of patients that were exposed to previous systemic therapies compared to the overall study population.

Table 10
Summary of PASI response, PGA response and percent of patients with all nails cleared at Weeks 10, 24 and 50. EXPRESS.

	Placebo → Infliximab 5 mg/kg (at week 24)	Infliximab 5 mg/kg
Week 10		
N	77	301
≥ 90% improvement	1 (1.3%)	172 (57.1%)[a]
≥ 75% improvement	2 (2.6%)	242 (80.4%)[a]
≥ 50% improvement	6 (7.8%)	274 (91.0%)
PGA of cleared (0) or minimal (1)	3 (3.9%)	242 (82.9%)[ab]
PGA of cleared (0), minimal (1), or mild (2)	14 (18.2%)	275 (94.2%)[ab]
Week 24		
N	77	276
≥ 90% improvement	1 (1.3%)	161 (58.3%)[a]
≥ 75% improvement	3 (3.9%)	227 (82.2%)[a]
≥ 50% improvement	5 (6.5%)	248 (89.9%)
PGA of cleared (0) or minimal (1)	2 (2.6%)	203 (73.6%)[a]
PGA of cleared (0), minimal (1), or mild (2)	15 (19.5%)	246 (89.1%)[a]
Week 50		
N	68	281
≥ 90% improvement	34 (50.0%)	127 (45.2%)

	Placebo → Infliximab 5 mg/kg (at week 24)	Infliximab 5 mg/kg
≥ 75% improvement	52 (76.5%)	170 (60.5%)
≥ 50% improvement	61 (89.7%)	193 (68.7%)
PGA of cleared (0) or minimal (1)	46 (67.6%)	149 (53.0%)
PGA of cleared (0), minimal (1), or mild (2)	59 (86.8%)	189 (67.3%)
All nails cleared [c]		
Week 10	1/65(1.5%)	16/235 (6.8%)
Week 24	3/65 (4.6%)	58/223 (26,0%) [a]
Week 50	27/64 (42.2%)	92/226 (40.7%)

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

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

Paediatric population

Paediatric Crohn's disease (6 to17 years)

In the REACH study, 112 patients (6 to 17 years, median age 13.0 years) with moderate to severe, active Crohn's disease (median paediatric CDAI of 40) and an inadequate response to conventional therapies were to receive 5 mg/kg infliximab at weeks 0, 2, and 6. All patients were required to be on a stable dose of 6-MP, AZA or MTX (35% were also receiving corticosteroids at baseline). Patients assessed by the investigator to be in clinical response at week 10 were randomised and received 5 mg/kg infliximab at either q8 weeks or q12 weeks as a maintenance treatment regimen. If response was lost during maintenance treatment, crossing over to a higher dose (10 mg/kg) and/or shorter dosing interval (q8 weeks) was allowed. Thirty two (32) evaluable paediatric patients crossed over (9 subjects in the q8 weeks and 23 subjects in the q12 weeks maintenance groups). Twenty four of these patients (75.0%) regained clinical response after crossing over.
The proportion of subjects in clinical response at week 10 was 88.4% (99/112). The proportion of subjects achieving clinical remission at week 10 was 58.9% (66/112).
At week 30, the proportion of subjects in clinical remission was higher in the q8 week (59.6%, 31/52) than the q12 week maintenance treatment group (35.3%, 18/51; p=0.013). At week 54, the figures were 55.8% (29/52) and 23.5% (12/51) in the q8 weeks and q12 weeks maintenance groups, respectively ($p < 0.001$).
Data about fistulas were derived from PCDAI scores. Of the 22 subjects that had fistulas at baseline, 63.6% (14/22), 59.1% (13/22) and 68.2% (15/22) were in complete fistula response at week 10, 30 and 54, respectively, in the combined q8 weeks and q12 weeks maintenance groups.

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

Paediatric ulcerative colitis (6 to 17 years)

The safety and efficacy of 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 severely 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 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.

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 medicinal product and returned for safety follow-up. At week 8, 45 patients were randomised and received 5 mg/kg infliximab at either q8 weeks or q12 weeks as a maintenance treatment regimen.
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 33.3% (17/51) as measured by the Paediatric Ulcerative Colitis Activity Index (PUCAI) score.

At week 54, the proportion of patients in clinical remission as measured by the PUCAI score was 38% (8/21) in the q8 week maintenance group and 18% (4/22) in the q12 week maintenance treatment group. For patients receiving corticosteroids at baseline, the proportion of patients in remission and not receiving corticosteroids at week 54 was 38.5% (5/13) for the q8 week and 0% (0/13) for the q12 week maintenance treatment group.

In this study, there were more patients in the 12 to 17 year age group than in the 6 to 11 year age group (45/60 vs.15/60). While the numbers of patients in each subgroup are too small to draw definitive conclusions about the effect of age, there was a higher number of patients in the younger age group who stepped up in dose or discontinued treatment due to inadequate efficacy.

Other paediatric indications

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing infliximab in all subsets of the paediatric population in rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis and Crohn's disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

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

Repeated administration of infliximab (5 mg/kg at 0, 2 and 6 weeks in fistulising Crohn´s disease, 3 or 10 mg/kg every 4 or 8 weeks in rheumatoid arthritis) resulted in a slight accumulation of infliximab in serum after the second dose. No further clinically relevant accumulation was observed. In most fistulising Crohn’s disease patients, infliximab was detected in serum for 12 weeks (range 4-28 weeks) after administration of the regimen.

Paediatric population

Population pharmacokinetic analysis based on data obtained from patients with ulcerative colitis (N=60), Crohn’s disease (N=112), juvenile rheumatoid arthritis (N=117) and Kawasaki disease (N=16) with an overall age range from 2 months to 17 years indicated that exposure to infliximab

was dependent on body weight in a non-linear way. Following administration of 5 mg/kg infliximab every 8 weeks, the predicted median steady-state infliximab exposure (area under concentration-time curve at steady state, AUC_{ss}) in paediatric patients aged 6 years to 17 years was approximately 20% lower than the predicted median steady-state drug exposure in adults. The median AUC_{ss} in paediatric patients aged 2 years to less than 6 years was predicted to be approximately 40% lower than that in adults, although the number of patients supporting this estimate is limited.

5.3 Preclinical safety data

Infliximab does not cross react with TNFα from species other than human and chimpanzees. Therefore, conventional preclinical safety data with infliximab are limited. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. In a fertility and general reproductive function study, the number of pregnant mice was reduced following administration of the same analogous antibody. It is not known whether this finding was due to effects on the males and/or the females. In a 6-month repeated dose toxicity study in mice, using the same analogous antibody against mouse TNFα, crystalline deposits were observed on the lens capsule of some of the treated male mice. No specific ophthalmologic examinations have been performed in patients to investigate the relevance of this finding for humans.
Long-term studies have not been performed to evaluate the carcinogenic potential of infliximab. Studies in mice deficient in TNFα demonstrated no increase in tumours when challenged with known tumour initiators and/or promoters.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Disodium hydrogen phosphate dihydrate
Sodium dihydrogen phosphate monohydrate
Polysorbate 80

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Before reconstitution:
The expiry date of the product is indicated on the packaging materials.

Storage conditions after reconstitution:
Chemical and physical in use stability of the reconstituted solution has been demonstrated for 24 hours at 25°C.

Storage conditions after reconstitution and dilution for infusion:
From a microbiological point of view, the product should be used as soon as possible but within 3 hours of reconstitution and dilution. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type 1 glass vial with a (butyl) rubber stopper and an aluminium seal with a flip-off button.
The pack contains 1 vial.

6.6 Special precautions for disposal and other handling

1. Calculate the dose and the number of Remsima 100 mg I.V. vials needed. Each Remsima 100 mg I.V. vial contains 100 mg infliximab. Calculate the total volume of reconstituted Remsima 100 mg I.V. solution required.

2. Under aseptic conditions, reconstitute each Remsima 100 mg I.V. vial with 10 ml of water for injections, using a syringe equipped with a 21-gauge (0.8 mm) or smaller needle. Remove flip-top from the vial and wipe the top with a 70% alcohol swab. Insert the syringe needle into the vial through the centre of the rubber stopper and direct the stream of water for injections to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilised powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. Check that the solution is colourless to light yellow and opalescent. The solution may develop a few fine translucent particles, as infliximab is a protein. The solution must not be used if opaque particles, discolouration, or other foreign particles are present.

3. The required volume of the reconstituted Remsima 100 mg I.V. solution should be diluted to 250 ml with sodium chloride 9 mg/mL (0.9%) solution for infusion. Do not dilute the reconstituted Remsima 100 mg I.V. solution with any other diluent. The dilution can be accomplished by withdrawing a volume of the sodium chloride 9 mg/mL (0.9%) solution for infusion from the 250-mL glass bottle or infusion bag equal to the volume of reconstituted Remsima 100 mg I.V.. The required volume of reconstituted Remsima 100 mg I.V. solution should slowly be added to the 250-mL infusion bottle or bag and gently be mixed. For volumes greater than 250 ml, either use a larger infusion bag (e.g. 500 ml, 1000 ml) or use multiple 250 ml infusion bags to ensure that the concentration of the infusion solution does not exceed 4 mg/ml.

4. Administer the infusion solution over a period of not less than the infusion time recommended (see section 4.2). Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 1.2 micrometer or less). Since no preservative is present, it is recommended that the administration of the solution for infusion is to be started as soon as possible and within 3 hours of reconstitution and dilution. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C. When reconstitution and dilution are performed under aseptic conditions, Remsima 100 mg I.V. infusion solution can be used within 24 hours if stored at 2°C to 8°C. Do not store any unused portion of the infusion solution for reuse.

5. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of infliximab with other agents. Do not infuse Remsima 100 mg I.V. concomitantly in the same intravenous line with other agents.

6. Visually inspect Remsima 100 mg I.V. for particulate matter or discolouration prior to administration. Do not use if visibly opaque particles, discolouration or foreign particles are observed.

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

7. Registration Holder

Padagis Israel Agencies Ltd.
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8. Manufacturer

Celltrion Inc, Incheon, South Korea

9. Registration number

15460.34158

Revised in May 2025.

25.5.25