SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Remsima 120 mg solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL single dose pre-filled pen contains 120 mg of infliximab*.

* Infliximab is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology.

Excipient(s) with known effect
Sorbitol 45 mg per 1 mL

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).
Clear to opalescent, colourless to pale brown solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Remsima, 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).

Crohn's disease

Remsima 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).

Ulcerative colitis

Remsima 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.

Ankylosing spondylitis

Remsima is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

Psoriatic arthritis

Remsima is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.

Remsima 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 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 ciclosporin, methotrexate or psoralen ultra-violet A (PUVA) (see section 5.1).

4.2 Posology and method of administration

Remsima treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of conditions for which Remsima is indicated. Patients treated with Remsima should be given the package leaflet and the patient reminder card. Instruction for use is provided in the package leaflet.

For subsequent injections and after proper training in subcutaneous injection technique, patients may self-inject with Remsima if their physician determines that it is appropriate and with medical follow-up as necessary. Suitability of the patient for subcutaneous home use should be assessed and patients should be advised to inform their healthcare professional if they experience symptoms of an allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see section 4.4).

During Remsima 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
Treatment with Remsima subcutaneous formulation should be initiated with loading doses of infliximab which may be intravenous or subcutaneous. When subcutaneous loading is used, Remsima 120 mg should be given as a subcutaneous injection followed by additional subcutaneous injections at 1, 2, 3 and 4 weeks after the first injection, then every 2 weeks thereafter. If intravenous loading doses of infliximab are given to initiate treatment, 2 intravenous infusions of infliximab 3 mg/kg should be given 2 weeks apart. The first treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the second intravenous administration. The recommended maintenance dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks.

Remsima must be given concomitantly with methotrexate.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment (see section 5.1).

Moderately to severely active Crohn's disease
The first treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of intravenous infusions. Before initiating treatment with Remsima subcutaneous formulation, 2 intravenous infusions of infliximab 5 mg/kg should be given at 2 weeks apart, and an additional intravenous infusion of infliximab 5 mg/kg may be given 4 weeks after the second infusion. The recommended maintenance dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient does not respond after loading doses of intravenous infliximab, 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.

Limited data in patients who initially responded to induction regimen with infliximab 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
The first treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of intravenous infusions. Before initiating treatment with Remsima subcutaneous formulation, 2 intravenous infusions of infliximab 5 mg/kg should be given at 2 weeks apart, and an additional intravenous infusion of infliximab 5 mg/kg may be given 4 weeks after the second infusion. The recommended maintenance dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient does not respond after loading doses of intravenous infliximab, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 14 weeks of the initial infusion.

Limited data in patients who initially responded to induction regimen with infliximab 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
The first treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of intravenous infusions. Before initiating treatment with Remsima subcutaneous formulation, 2 intravenous infusions of infliximab 5 mg/kg should be given at 2 weeks apart, and an additional intravenous infusion of infliximab 5 mg/kg may be given 4 weeks after the second infusion. The recommended maintenance dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks.

Available data suggest that the clinical response is usually achieved within 14 weeks of treatment (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Ankylosing spondylitis
Treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient does not respond by 6 weeks (i.e. after 2 intravenous infusions), no additional treatment with infliximab should be given.

Psoriatic arthritis
Treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks.

Psoriasis
Treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient shows no response after 14 weeks (i.e. 2 intravenous infusions and 5 subcutaneous injections), no additional treatment with infliximab should be given.

Re-administration for Crohn's disease and rheumatoid arthritis
From experience with intravenous infliximab, if the signs and symptoms of disease recur, infliximab can be re-administered within 16 weeks following the last administration. In clinical studies with intravenous infliximab, 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
From experience with intravenous infliximab, 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
From experience with intravenous infliximab, 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
From experience with intravenous infliximab, 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 intravenous 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 of intravenous infliximab 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 of intravenous infliximab (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 of intravenous infliximab is not recommended (see section 4.8). In this situation, infliximab should be re-initiated as a single dose of intravenous infliximab followed by the maintenance dose recommendations of subcutaneous infliximab described above given 4 weeks after the last administration of intravenous infliximab.

Switching to and from Remsima subcutaneous formulation across indications
When switching from the maintenance therapy of infliximab intravenous formulation to the subcutaneous formulation of Remsima, the subcutaneous formulation may be administered at the time of next planned administration of the intravenous infusions of infliximab.

There is insufficient information regarding the switching of patients who received the intravenous infusions of infliximab higher than 3 mg/kg for rheumatoid arthritis or 5 mg/kg for Crohn's disease every 8 weeks to the subcutaneous formulation of Remsima.

Information regarding switching patients from the subcutaneous formulation to the intravenous formulation of Remsima is not available.

Missed dose

If patients miss an injection of Remsima subcutaneous formulation, they should be instructed to take the missed dose immediately in case this happens within 7 days from the missed dose, and then remain on their original dosing schedule. If the dose is delayed by 8 days or more, the patients should be instructed to skip the missed dose, wait until their next scheduled dose, and then remain on their original dosing schedule.

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 with infliximab intravenous formulations and the same is expected for subcutaneous formulation. 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

The safety and efficacy of Remsima subcutaneous therapy in children aged below 18 years of age have not yet been established. No data are available. Therefore, subcutaneous use of Remsima is recommended for use only in adults.

Method of administration

Remsima 120 mg solution for injection in pre-filled pen is administered by subcutaneous injection only. Full instructions for use are provided in the package leaflet. For the two initial intravenous infusions, 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). The physician should ensure appropriate follow-up of patients for any systemic injection reaction and localised injection site reaction after the initial subcutaneous injection is administered.

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.

Systemic injection reaction/ localised injection site reaction/ hypersensitivity

Infliximab has been associated with systemic injection reactions, anaphylactic shock and delayed hypersensitivity reactions (see section 4.8).

Acute reactions including anaphylactic reactions may develop during (within seconds) or within a few hours following administration of infliximab. If acute reactions occur, medical treatment should be sought immediately. For this reason, the initial intravenous administrations should take place where emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway is immediately available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.

Localised injection site reactions predominantly of mild to moderate in nature included the following reactions limited to injection site: erythema, pain, pruritus, swelling, induration, bruising, haematoma, oedema, coldness, paraesthesia, haemorrhage, irritation, rash, ulcer, urticaria, application site vesicles and scab were reported to be associated with infliximab subcutaneous treatment. Most of these reactions may occur immediately or within 24 hours after subcutaneous injection. Most of these reactions resolved spontaneously without any treatment.

Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions when administered by intravenous infusion. 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 with intravenously administered infliximab. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and in the case of intravenously administered infliximab, 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 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 (TNFα) mediates inflammation and modulates cellular immune responses. Experimental data show that TNFα is essential for the clearing of intracellular infections. Clinical experience shows that host defence against infection is compromised in some patients treated with infliximab.

It should be noted that suppression of TNFα 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 reminder 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 $\geq$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 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 titers 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 infliximab 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 live vaccines to infants exposed *in utero* to infliximab. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier

timepoint if there is a clear clinical benefit for the individual infant (see section 4.6).

Infant exposure via breast milk

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

Therapeutic infectious agents

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

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 infliximab and is positive for antibodies against double-stranded DNA, further treatment with infliximab 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 infliximab therapy. Discontinuation of infliximab 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.

Although subcutaneous administration is not indicated for children under age of 18 years, it should be noted that 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 infliximab, 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

Infliximab should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and infliximab 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, leukopenia, 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 infliximab therapy should be considered in patients with confirmed significant haematologic abnormalities.

Others

There is limited safety experience of infliximab treatment in patients who have undergone surgical procedures, including arthroplasty. 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 infections, and appropriate actions should be taken.

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 infliximab-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).

Sodium and sorbitol contents

Remsima contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’ and 45 mg sorbitol per 1 mL (in each 120 mg dose).

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 infliximab with other biological therapeutics used to treat the same conditions as infliximab, including anakinra and abatacept, is not recommended (see section 4.4).

It is recommended that live vaccines not be given concurrently with Remsima. It is also recommended that live vaccines not be given to infants after in utero exposure to infliximab for 12 months following birth. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant (see section 4.4).

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see sections 4.4 and 4.6).
It is recommended that therapeutic infectious agents not be given concurrently with infliximab (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 infliximab treatment.

Pregnancy

The moderate number of prospectively collected pregnancies exposed to infliximab resulting in live birth with known outcomes, including approximately 1,100 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 live vaccines (e.g. BCG vaccine) to infants exposed to infliximab *in utero* is not recommended for 12 months after birth (see sections 4.4 and 4.5). If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant. 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, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Infliximab 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 may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of infliximab (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 with infliximab, 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, sarcoidosis/sarcoid-like reaction, intestinal or perianal abscess (in Crohn's disease) and serious infusion reactions (see section 4.4).

The safety profile of Remsima subcutaneous formulation from active rheumatoid arthritis (evaluated in 168 and 175 patients for the subcutaneous infliximab group and the intravenous infliximab group, respectively), active Crohn's disease (evaluated in 297, 38 and 105 patients for the subcutaneous infliximab group, the intravenous infliximab group and the placebo group, respectively) and active ulcerative colitis patients (evaluated in 334, 40 and 140 patients for the subcutaneous infliximab group, the intravenous infliximab group and the placebo group, respectively) was overall similar to the safety profile of the intravenous formulation.

Tabulated list of adverse reactions

Table 1 lists the 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
Adverse reactions in clinical studies and from post-marketing experience of infliximab

Infections and infestations	
Very common:	Viral infection (e.g. influenza, herpes virus infection, COVID-19*).
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 and ulcerative colitis), Merkel cell carcinoma, Kaposi's sarcoma.
Blood and lymphatic system disorders	
Common:	Neutropenia, leukopenia, 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.

* COVID-19 was seen with the SC administered Remsima

** 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

Systemic injection reaction and localised injection site reaction in adult patients administered with Remsima subcutaneous formulation

The safety profile of Remsima subcutaneous formulation in combination with methotrexate was evaluated in a Phase I/III parallel group study in patients with active rheumatoid arthritis. The safety population consisted of 168 patients in the Remsima subcutaneous group and 175 patients in the Remsima intravenous group. For study details, see Section 5.1.

The incidence rate of systemic injection reactions (e.g. rash, pruritus, flushing and oedema) was 1.2 patients per 100 patient-years in the Remsima subcutaneous group (from Week 6) and 2.1 patients per 100 patient-years in the Remsima intravenous group who switched to Remsima subcutaneous administration (from Week 30). All systemic injection reactions were mild to moderate.

The incidence rate of localised injection site reactions (e.g. injection site erythema, pain, pruritus and swelling) was 17.6 patients per 100 patient-years in the Remsima subcutaneous group (from Week 6) and 21.4 patients per 100 patient-years in those who switched to Remsima subcutaneous administration (from Week 30). Most of these reactions were mild to moderate and resolved spontaneously without any treatment within a day.

In the integrated analysis including a Phase I study conducted in patients with active Crohn’s disease and active ulcerative colitis, a Phase III study conducted in patients with active Crohn’s disease and a Phase III study conducted in patients with active ulcerative colitis, the safety population consisted of 631 patients in the Remsima subcutaneous group (297 patients with active Crohn’s disease and 334 patients with active ulcerative colitis) and 245 patients in the Placebo group (105 patients with active Crohn’s disease and 140 patients with active ulcerative colitis). For study details, see Section 5.1.

The incidence rate of systemic injection reactions (e.g. nausea and dizziness) was 3.56 patients per 100 patient-years in the Remsima subcutaneous group.

The incidence rate of localised injection site reactions (e.g. injection site erythema, pain, pruritus, bruising) was 8.68 patients per 100 patient-years in the Remsima subcutaneous group. Most of these reactions were mild to moderate and mostly resolved spontaneously without any treatment within a few days.

In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal oedema and severe bronchospasm, and seizure have been associated with infliximab intravenous 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.

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 with intravenous infliximab, 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 of IV infliximab in patients with Crohn's disease (ACCENT I study), the incidence of serum sickness-like reactions was 2.4%.

Immunogenicity

Intravenous formulation

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: "Systemic injection reaction/ localised injection site reaction/ hypersensitivity").

Because immunogenicity analyses are assay-specific, comparison of the incidence of antibodies to infliximab reported in this section with the incidence of antibodies in other studies may be misleading.

Subcutaneous formulation

In rheumatoid arthritis patients on maintenance treatment, the incidence of anti-infliximab antibodies following the subcutaneous infliximab was demonstrated to be not higher than that of the intravenous infliximab and anti-infliximab antibodies had no significant impact on efficacy (determined by disease activity score in 28 joints [DAS28] and American College of Rheumatology criteria 20 [ACR20]) and the safety profile.

In Crohn's disease and ulcerative colitis patients on maintenance treatment, the incidence of anti-infliximab antibodies was not higher in patients who received subcutaneous infliximab in comparison to those who received intravenous infliximab. In Crohn’s disease and ulcerative colitis patients, there was a correlation between loss of response and anti-infliximab antibodies, while anti-infliximab antibodies had no significant impact on the safety profile.

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 $\leq$35%) were treated with 3 infusions of infliximab 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 38 weeks, 9 of 101 patients treated with infliximab (2 at 5 mg/kg and 7 at 10 mg/kg) died compared to one death among the 49 patients on placebo.

There have been post-marketing reports of 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 using intravenous infliximab

Indication	Number of patients[3]		Median follow-up (wks)[4]		≥ 3 x ULN		≥ 5 x ULN	
	placebo	infliximab	placebo	infliximab	placebo	infliximab	placebo	infliximal
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%
Ulcerative colitis	242	482	30.1	30.8	1.2%	2.5%	0.4%	0.6%
Ankylosing spondylitis	76	275	24.1	101.9	0.0%	9.5%	0.0%	3.6%
Psoriatic arthritis	98	191	18.1	39.1	0.0%	6.8%	0.0%	2.1%
Plaque psoriasis	281	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 randomised 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).

Other 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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Single intravenous doses up to 20 mg/kg have been administered without toxic effects and repeated doses of Remsima subcutaneous formulation up to 240 mg have been administered without toxic effects. There is no specific treatment for Remsima overdose. In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, tumour necrosis factor alpha (TNFα) 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 TNFα but not to lymphotoxin α (TNFβ).

Pharmacodynamic effects

Infliximab inhibits the functional activity of TNFα 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 TNFα and when administered after disease onset, it allowed eroded joints to heal. *In vivo*, infliximab rapidly forms stable complexes with human TNFα, a process that parallels the loss of TNFα 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 TNF_{α}. 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 TNF_{α} and interferon γ. 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

Intravenous formulation

The efficacy of infliximab intravenous formulation 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 anti-inflammatory drugs (NSAIDs) was permitted.

The primary endpoints were the reduction of signs and symptoms as assessed by the ACR 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%)

		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]
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 3 mg/kg and 6 mg/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.

Subcutaneous formulation

The efficacy of subcutaneous infliximab in rheumatoid arthritis patients was assessed in a randomised, parallel-group pivotal Phase I/III study consisting of two parts: Part 1 to determine the optimal dose of subcutaneous infliximab and Part 2 to demonstrate non-inferiority in terms of efficacy of subcutaneous infliximab compared to intravenous infliximab treatment in a double-blind setting.

In Part 2 of this study, among 357 patients who were enrolled to receive 2 doses of Remsima 3 mg/kg intravenously at Weeks 0 and 2, 167 patients were randomised to receive Remsima 120 mg subcutaneously at Week 6 and every 2 weeks up to Week 54, while 176 patients were randomised to receive Remsima 3 mg/kg intravenously at Weeks 6, 14 and 22 and then switched to Remsima 120 mg subcutaneous at Week 30 once-every 2 weeks up to Week 54. Methotrexate was given concomitantly.

The primary endpoint of the study was the treatment difference of the change from baseline of DAS28 (CRP) at Week 22. The estimate of treatment difference was 0.27 with corresponding lower limit of the two-sided 95% confidence interval [CI] of 0.02 (95% CI: 0.02, 0.52), which was greater than the pre-specified non-inferiority margin of -0.6 indicating non-inferiority of Remsima subcutaneous formulation to Remsima intravenous formulation.

The analysis of other efficacy endpoints showed that efficacy profile of Remsima subcutaneous formulation compared to Remsima intravenous formulation in RA patients was generally comparable in terms of disease activity measured by DAS28 (CRP and ESR) and ACR response up to Week 54. The mean scores for DAS28 (CRP) and DAS28 (ESR) gradually decreased from baseline at each time point until Week 54 in each treatment arm (see Table 5 and Table 6, respectively).

Table 5
Mean (SD) Actual Values of DAS28 (CRP and ESR)

	DAS28 (CRP)		**DAS28 (ESR)**	
Visit	**Remsima IV 3 mg/kg[b] (N=174)**	**Remsima SC 120 mg (N=165)**	**Remsima IV 3 mg/kg[b] (N=174)**	**Remsima SC 120 mg (N=165)**
Baseline	5.9 (0.8)	6.0 (0.8)	6.6 (0.8)	6.7 (0.8)
Week 6	4.1 (1.2)	4.0 (1.2)	4.8 (1.3)	4.6 (1.2)
Week 22	3.5 (1.2)[a]	3.3 (1.1)[a]	4.1 (1.3)	4.0 (1.1)

Visit	DAS28 (CRP)		DAS28 (ESR)	
	Remsima IV 3 mg/kg[b] (N=174)	**Remsima SC 120 mg (N=165)**	**Remsima IV 3 mg/kg[b] (N=174)**	**Remsima SC 120 mg (N=165)**
Week 54	2.9 (1.2)[b]	2.8 (1.1)	3.4 (1.3)[b]	3.4 (1.2)

a Two-sided 95% CI for difference in the mean change from baseline for DAS28 (CRP) at Week 22 was well above the pre-defined non-inferiority margin of -0.6
b Remsima IV was switched to Remsima SC at Week 30

Table 6
Proportions of Patients Achieving Clinical Response According to the ACR Criteria

Visit	ACR20		ACR50		ACR70	
	Remsima IV 3 mg/kg[a] (N=174)	**Remsima SC 120 mg (N=165)**	**Remsima IV 3 mg/kg[a] (N=174)**	**Remsima SC 120 mg (N=165)**	**Remsima IV 3 mg/kg[a] (N=174)**	**Remsima SC 120 mg (N=165)**
Week 6	103 (59.2%)	107 (64.8%)	45 (25.9%)	47 (28.5%)	18 (10.3%)	19 (11.5%)
Week 22	137 (78.7%)	139 (84.2%)	90 (51.7%)	85 (51.5%)	49 (28.2%)	46 (27.9%)
Week 54	125 (71.8%)[a]	132 (80.0%)	101 (58.0%)[a]	108 (65.5%)	68 (39.1%)[a]	77 (46.7%)

a Remsima IV was switched to Remsima SC at Week 30

There are no clinical trials with Remsima 120 mg given subcutaneously without intravenous loading doses of infliximab in patients with rheumatoid arthritis. However, population pharmacokinetic and pharmacokinetic/pharmacodynamic modelling and simulation predicted comparable infliximab exposure (AUC over 8 weeks) and efficacy (DAS28 and ACR20 response) from Week 6 onward in rheumatoid arthritis patients treated with Remsima 120 mg given without intravenous loading doses of infliximab when compared with Remsima 3 mg/kg given intravenously at Weeks 0, 2 and 6, and then every 8 weeks.

Adult Crohn's disease

Intravenous formulation

Induction treatment in moderately to severely active Crohn's disease
The efficacy of a single dose treatment with infliximab intravenous formulation was assessed in 108 patients with active Crohn's disease (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 intravenous 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 7). 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 7
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 8. 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 8
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 intravenous formulation 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 intravenous 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 9). Corticosteroid tapering was permitted after week 6.

Table 9
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.

Subcutaneous formulation

The efficacy of subcutaneous infliximab in active Crohn's disease and active ulcerative colitis patients was assessed in an open-label, randomised, parallel-group, Phase I study consisting of two parts: Part 1 to determine the optimal dose of subcutaneous infliximab and Part 2 to demonstrate non-inferiority in terms of PK of subcutaneous infliximab compared to intravenous infliximab treatment.

In Part 1 of this study, 45 patients with active Crohn's disease were enrolled to receive 2 doses of Remsima 5 mg/kg intravenously at Weeks 0 and 2 and subsequently 44 patients were randomised into four cohorts to receive Remsima 5 mg/kg intravenously (n=13) at Week 6 and every 8 weeks up to Week 54, Remsima 120 mg subcutaneously (n=11), Remsima 180 mg subcutaneously (n=12) or Remsima 240 mg subcutaneously (n=8) at Week 6 and every 2 weeks up to Week 54.

In Part 2 of this study, among 136 patients (57 patients with active Crohn's disease and 79 patients with active ulcerative colitis) who were enrolled to receive 2 doses of Remsima 5 mg/kg intravenously at Weeks 0 and 2, 66 patients (28 patients with active Crohn's disease and 38 patients with active ulcerative colitis) were randomised to receive Remsima 120/ 240 mg subcutaneously at Week 6 and every 2 weeks up to Week 54, while 65 patients (25 patients with active Crohn's disease and 40 patients with active ulcerative colitis) were randomised to receive Remsima 5 mg/kg intravenously at Week 6, 14 and 22 and then switched to Remsima 120/ 240 mg subcutaneous formulation at Week 30 once-every 2 weeks up to Week 54. The dosage of Remsima 120/ 240 mg subcutaneous formulation was determined based on the patient's body weight at Week 6 for those who received Remsima subcutaneously and at Week 30 for those who switched to Remsima subcutaneous formulation (Remsima subcutaneous 120 mg for patients <80 kg; 240 mg for patients ≥80 kg).

In active Crohn's disease patients, the descriptive efficacy results following Remsima 120 mg subcutaneous formulation were generally comparable to Remsima 5 mg/kg intravenous formulation in terms of clinical response (CDAI-70 response defined as a decrease in CDAI by ≥70 points and CDAI-100 response defined as ≥100 points from baseline), clinical remission (defined as an absolute CDAI score of <150 points) and endoscopy assessments (endoscopic response defined as a decrease in ≥50% of overall Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) score from the baseline value and endoscopic remission defined as an absolute SES-CD score of ≤2 points).

The efficacy of subcutaneous infliximab in active Crohn's disease patients was also assessed in a randomized, double-blind, placebo-controlled clinical study in 343 adult patients with moderately to severely active CD (CDAI of 220 to 450 points) with an inadequate response to conventional therapies (LIBERTY-CD). Concomitant treatment with stable doses of aminosalicylates, corticosteroids, antibiotics and/or immunomodulatory agents were permitted. Corticosteroids dose was tapered after Week 10. Patients who were classified as CDAI-100 responders at Week 10 following three IV infusions of infliximab 5 mg/kg at Weeks 0, 2 and 6 were randomized to receive an injection of either subcutaneous infliximab 120 mg or placebo every 2 weeks thereafter from Week 10 through Week 54.

The co-primary endpoints were clinical remission (based on CDAI) and endoscopic response at Week 54. Clinical remission was defined as an absolute CDAI score of <150 points, and endoscopic response was defined as a 50% decrease in SES-CD score from the baseline value.
Key secondary endpoints were CDAI -100 response and endoscopic remission at Week 54.

In LIBERTY-CD, patients treated with subcutaneous infliximab at the recommended dosage (120 mg every 2 weeks) achieved clinical remission (based on CDAI), endoscopic response, CDAI-100 response, and endoscopic remission more often compared to placebo (Table 10).

Table 10
Clinical Remission, Endoscopic Response, CDAI-100 Response and Endoscopic Remission in LIBERTY-CD

Endpoint[a]	Infliximab sc 120 mg (N=231)	Placebo (N=112)	Treatment Difference and 95% CI
Clinical remission (based on CDAI) at Week 54[b]	62.3%	32.1%	32.1% (20.9, 42.1)
Endoscopic response at Week 54[c]	51.1%	17.9%	34.6% (24.1, 43.5)
CDAI-100 response at Week 54[d]	65.8%	38.4%	28.9% (17.7, 39.2)
Endoscopic remission at Week 54[e]	34.6%	10.7%	24.9% (15.4, 32.8)

a Patient who had loss of response between Week 22 and 54 were allowed to switch to 240 mg infliximab sc both in the infliximab and placebo arms. The patients who switched are considered non-responders.
b Defined as an absolute CDAI score of <150 points.
c Defined as a 50% decrease in SES-CD score from the baseline value.
d Defined as a decrease in CDAI score of 100 points or more from the baseline value.
e Defined as an absolute SES-CD score of ≤4 and at least 2-point reduction from the baseline value with no sub-score of >1.

In LIBERTY-CD, dose adjustment to subcutaneous infliximab 240 mg was allowed from Week 22 for patients who initially responded but then lost response in both subcutaneous infliximab 120 mg and placebo groups. Loss of response was defined as an increase in CDAI of ≥100 points from the Week 10 CDAI score with a total score ≥220. Among patients who were responders to intravenous infliximab at week 10, who met loss of response criteria at or after week 22 and received a dose increase to subcutaneous infliximab 240 mg, 21/34 (61.8%) had regained CDAI-100 response at Week 54. Spontaneous regain of response, without dose adjustment, occurred in 1/7 patients in each group (infliximab sc 120 mg and placebo). Including an open-label extension phase of the LIBERTY-CD study, overall 73 patients have received infliximab 240 mg as maintenance treatment for at least 44 weeks with no relevant additional safety findings compared to the 120 mg dose.

In LIBERTY-CD, the impact of use of immunosuppressant (azathioprine, 6-mercaptopurine and methotrexate) on efficacy was evaluated. There was no significant difference between patients with and without immunosuppressants in the primary and the key secondary efficacy endpoints.

Adult ulcerative colitis

Intravenous formulation

The safety and efficacy of intravenous 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 11
Effects on clinical response, clinical remission and mucosal healing at Weeks 8 and 30. Combined data from ACT 1 & 2

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subjects 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, ACT 1 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.

Subcutaneous formulation

The efficacy of subcutaneous infliximab in active ulcerative colitis patients was assessed in Part 2 of an open-label, randomised, parallel-group, Phase I study. For study details, see Section 5.1 on Crohn's disease, subcutaneous formulation.

In active ulcerative colitis patients, the descriptive efficacy results following Remsima 120 mg subcutaneous formulation were generally comparable to Remsima 5 mg/kg intravenous formulation in terms of clinical response (defined as a decrease from baseline in total Mayo score of at least 3 points and at least 30% or a decrease from baseline in partial Mayo score at least 2 points, with an accompanying decrease from baseline in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1), clinical remission (defined as a total Mayo score of ≤2 points with no individual subscore exceeding 1 point, or partial Mayo score of ≤1 point) and mucosal healing (defined as absolute endoscopic subscore of 0 or 1 from Mayo Scoring System).

Adult ankylosing spondylitis

Intravenous formulation

Efficacy and safety of infliximab intravenous formulation 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

Intravenous formulation

Efficacy and safety of infliximab intravenous formulation 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 12 below:

Table 12
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

Intravenous formulation

The efficacy of infliximab intravenous formulation 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 5 mg/kg group and 13.8% of patients in the 3 mg/kg group were PASI 75 responders. Between weeks 6 and 26, symptoms of psoriasis gradually returned with a median time to disease relapse of >20 weeks. No rebound was observed.

EXPRESS evaluated the efficacy of infliximab induction and maintenance therapy in 378 patients with plaque psoriasis. Patients received 5 mg/kg infliximab- or placebo-infusions at weeks 0, 2 and 6 followed by maintenance therapy every 8 weeks through week 22 in the placebo group and through week 46 in the infliximab group. At week 24, the placebo group crossed over to infliximab induction therapy (5 mg/kg) followed by infliximab maintenance therapy (5 mg/kg). Nail psoriasis was assessed using the Nail Psoriasis Severity Index (NAPSI). Prior therapy with PUVA, methotrexate, ciclosporin, or acitretin had been received by 71.4% of patients, although they were not necessarily therapy resistant. Key results are presented in Table 13. 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 13
Summary of PASI response, PGA response and percent of patients with all nails cleared at Weeks 10, 24 and 50. EXPRESS

	Placebo → Infliximab 5 mg/kg (at week 24)	Infliximab 5 mg/kg
Week 10		
N	77	301
≥90% improvement	1 (1.3%)	172 (57.1%) [a]
≥75% improvement	2 (2.6%)	242 (80.4%) [a]
≥50% improvement	6 (7.8%)	274 (91.0%)
PGA of cleared (0) or minimal (1)	3 (3.9%)	242 (82.9%) [ab]
PGA of cleared (0), minimal (1), or mild (2)	14 (18.2%)	275 (94.2%) [ab]
Week 24		
N	77	276
≥90% improvement	1 (1.3%)	161 (58.3%) [a]
≥75% improvement	3 (3.9%)	227 (82.2%) [a]
≥50% improvement	5 (6.5%)	248 (89.9%)
PGA of cleared (0) or minimal (1)	2 (2.6%)	203 (73.6%) [a]
PGA of cleared (0), minimal (1), or mild (2)	15 (19.5%)	246 (89.1%) [a]
Week 50		
N	68	281
≥90% improvement	34 (50.0%)	127 (45.2%)
≥75% improvement	52 (76.5%)	170 (60.5%)
≥50% improvement	61 (89.7%)	193 (68.7%)
PGA of cleared (0) or minimal (1)	46 (67.6%)	149 (53.0%)
PGA of cleared (0), minimal (1), or mild (2)	59 (86.8%)	189 (67.3%)
All nails cleared[c]		
Week 10	1/65(1.5%)	16/235 (6.8%)
Week 24	3/65 (4.6%)	58/223 (26.0%) [a]
Week 50	27/64 (42.2%)	92/226 (40.7%)

	Placebo → Infliximab 5 mg/kg (at week 24)	Infliximab 5 mg/kg

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

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

Absorption and distribution

Single subcutaneous injections of 120, 180 and 240 mg of infliximab yielded approximately dose proportional increases in the maximum serum concentration (C_{max}) and area under the concentration-time curve (AUC). The apparent volume of distribution during the terminal phase (mean of 7.3 to 8.8 litres) was not dependent on the administered dose.

After single doses of 120, 180 and 240 mg of subcutaneous infliximab administered to healthy subjects, the mean C_{max} values were 10.0, 15.1 and 23.1 µg/mL, respectively, and for all doses infliximab could be detected in the serum for at least 12 weeks thereafter.

The bioavailability of subcutaneous infliximab, estimated in a population PK model, was 62% (95% CI: 60% - 64%).

After administration of infliximab 120 mg subcutaneously every 2 weeks (from Week 6 after 2 doses of intravenous infliximab at Weeks 0 and 2) to patients with active rheumatoid arthritis who were concomitantly treated with MTX, the median (CV%) C_{trough} level at Week 22 (steady state) was 12.8 µg/mL (80.1%).

After administration of infliximab 120 mg subcutaneously every 2 weeks (from Week 6 after 2 doses of intravenous infliximab at Weeks 0 and 2) to patients with active Crohn's disease and active ulcerative colitis, the median (CV%) C_{trough} level at Week 22 (steady state) was 20.1 µg/mL (48.9%).

Based on PK results from clinical studies in patients with active rheumatoid arthritis, active Crohn's disease and active ulcerative colitis and population PK modelling, C_{trough} levels at steady state would be higher after administration of infliximab 120 mg subcutaneous formulation given every 2 weeks compared with infliximab 5 mg/kg intravenous formulation given every 8 weeks.

For the dosing regimen with subcutaneous loading in patients with rheumatoid arthritis, the predicted median AUC value was 17,400 μg·h/mL from Week 0 to 6 which was approximately 1.8 fold lower than the predicted median AUC value for the dosing regimen with infliximab intravenous loading doses (32,100 μg·h/mL). Whereas, the predicted median AUC values from Week 6 to 14 were comparable between the two dosing regimens with subcutaneous loading and intravenous loading (19,600 and 18,100 μg·h/mL, respectively).

Elimination

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.

In studies in healthy subjects, the mean (± SD) apparent clearance of Remsima 120 mg administered subcutaneously was 19.3 ± 6.9 mL/hr.

In the RA patients, the mean (± SD) apparent clearance of Remsima 120 mg subcutaneous at steady state was 18.8 ± 8.3 mL/hr. In the active Crohn's disease and active ulcerative colitis patients, the mean (± SD) apparent clearance of Remsima 120 mg subcutaneous at steady state was 16.1 ± 6.9 mL/hr.

The mean terminal half-life ranged from 11.3 days to 13.7 days for 120, 180 and 240 mg of subcutaneous infliximab administered to healthy subjects.

Special populations

Elderly

The pharmacokinetics of infliximab injected via subcutaneous route in elderly patients has not been studied.

Paediatric population

Subcutaneous administration of Remsima is not recommended for paediatric use and no data are available on the use of Remsima administered subcutaneously in the paediatric population.

Hepatic and renal impairment

Studies with infliximab have not been performed in patients with liver or renal disease.

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.

The subcutaneous administration of Remsima to New Zealand White rabbits was well tolerated at the actual concentration to be used in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid
Sodium acetate trihydrate
Sorbitol
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze. Keep the pre-filled pen in the outer carton in order to protect from light.

The medicinal product may be stored at temperatures up to a maximum of 25°C for a period of up to 28 days. The medicinal product must be discarded if not used within the 28-day period.

6.5 Nature and contents of container

Remsima 120 mg solution for injection in single-use pre-filled pen. The syringe inside the pen is made from type 1 glass with a plunger stopper (flurotec-coated elastomer) and needle with a rigid needle shield.

Packs of:

- 1 prefilled pen (1 mL sterile solution) with 2 alcohol pads.
- 2 prefilled pens (1 mL sterile solution) with 2 alcohol pads.
- 4 prefilled pens (1 mL sterile solution) with 4 alcohol pads.
- 6 prefilled pens (1 mL sterile solution) with 6 alcohol pads.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Remsima is a solution that is clear to opalescent, colourless to pale brown. Do not use if the solution is cloudy, discoloured or contains visible particulate matter.

After use, place the pre-filled pen into a puncture resistant container and discard as required by local regulations. Do not recycle the injecting device. Always keep the medicinal product out of the sight and reach of children.

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

7. MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PLGB 51808/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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