1. NAME OF THE MEDICINAL PRODUCT

Remsima 120 mg solution for subcutaneous injection in pre-filled syringe
Remsima 120 mg solution for subcutaneous injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Remsima 120 mg solution for subcutaneous injection in pre-filled syringe
Each 1 mL single dose pre-filled syringe contains 120 mg of infliximab*.

Remsima 120 mg solution for subcutaneous injection in pre-filled pen
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 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 ankylosing spondylitis, in patients who have severe axial symptoms, elevated serological markers of inflammatory activity and who have responded inadequately to conventional therapy.

Psoriatic arthritis

Remsima in combination with methotrexate, is indicated for:
Treatment of active and progressive psoriatic arthritis in patients who have responded inadequately to disease-modifying anti-rheumatoid drugs.

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 patient information leaflet. Instruction for use is provided in the patient information 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
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 within 2 weeks to the initial infusion, no additional treatment with infliximab should be given.

Fistulising Crohn's disease
Treatment with Remsima 120 mg 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 after 6 doses (i.e. 2 intravenous infusions and 4 subcutaneous injections), no additional treatment with infliximab should be given.

Ulcerative colitis
Treatment with Remsima 120 mg 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.

Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. 2 intravenous infusions and 4 subcutaneous injections (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 120 mg 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 of 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 120 mg 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 120 mg 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. 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. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks.

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 retreatment 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).

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 8 weeks after the last 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 bi-weekly 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 bi-weekly 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 syringe or in pre-filled pen are administered by subcutaneous injection only. Full instructions for use are provided in the patient information 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

Remsima is a biosimilar medicinal product. The prescribing physician should be involved in any decision regarding its interchangeability.

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded (or stated) in the patient file.
Remsima is contraindicated in patients with tuberculosis. Before starting treatment with Remsima, patients must be evaluated for both active and inactive ('latent') tuberculosis (see *Infections*).

Remsima is contraindicated in patients with moderate or severe heart failure (NYHA Class III/IV), and it should be used with caution in patients with mild heart failure (NYHA Class I/II) (see *Heart failure*).

Systemic injection reaction/ localised injection site reaction and hypersensitivity
Infliximab has been associated with acute infusion-related reactions, including, anaphylactic shock, and delayed hypersensitivity reactions (see section 4.8 *Adverse Reactions*). 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.
Acute infusion reactions including anaphylactic reactions may develop during (within seconds) or within a few hours following infusion. If acute infusion reactions occur, the infusion must be interrupted immediately. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Patients may be pretreated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.

Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions. A low proportion of the infusion reactions were serious allergic reactions. In Crohn's disease patients, an association between development of antibodies to infliximab and reduced duration of response has also been observed. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and a reduction in the frequency of infusion reactions. The effect of concomitant immunomodulator therapy was more profound in episodically treated patients than in patients given maintenance therapy. Patients who 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 Remsima infusions must not be administered (see section 4.8 *Adverse Reactions*).

In clinical trials, delayed hypersensitivity reaction has been reported. Available data suggest an increased risk for delayed hypersensitivity with increasing drug free interval. Advise patients to seek immediate medical advice if they experience any delayed adverse event (see section 4.8 *Adverse Reactions*). If patients are retreated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.

Infusion reactions following re-administration of infliximab: In a psoriasis clinical trial, a 3-dose re-induction of infliximab after a period of no treatment resulted in a higher incidence of serious infusion reactions during the re-induction regimen (see section 4.8 *Adverse Reactions*) than had been observed in rheumatoid arthritis, psoriasis, and Crohn's disease trials in which a period of no drug treatment was followed by regular maintenance therapy without re-induction. In general, the benefit-risk of re-administration of infliximab after a period of no-treatment, especially as a re-induction regimen given at weeks 0, 2, and 6 should be carefully considered.

Infections

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

Caution should be exercised when considering the use of Remsima in patients with chronic infection or a history of recurrent infections, including use of concomitant immunosuppressive medications. 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 also mask symptoms of infection such as fever. Early recognition of atypical clinical presentations of serious infections is critical in order to minimize delays in diagnosis and treatment.

Tuberculosis, viral infections, bacterial infections, including sepsis and pneumonia, invasive fungal infections, and other opportunistic infections have been observed in patients treated with infliximab. Some of these infections have been fatal.

Cases of active tuberculosis have occurred in patients treated with infliximab during and after treatment for latent tuberculosis. Cases of active tuberculosis including miliary tuberculosis and tuberculosis with extrapulmonary location have been reported in patients treated with infliximab.

Opportunistic infections reported in patients on infliximab have included, but are not limited to pneumocystosis, histoplasmosis, cytomegalovirus infection, atypical mycobacterial infections listeriosis and aspergillosis. 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 Remsima, should be monitored closely and undergo a complete diagnostic evaluation. Administration of Remsima should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial and antifungal therapy should be initiated until the infection is controlled.

In clinical trials, infections have been reported more frequently in paediatric patient populations than in adult populations (see section 4.8 *Adverse Reactions*).

Before starting treatment with Remsima, 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, i.e. tuberculin skin test and chest x-ray, should be performed in all patients (local recommendations may apply). 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, Remsima therapy must not be initiated (see section 4.3).

If inactive ('latent') tuberculosis is diagnosed, prophylactic anti-tuberculosis therapy must be started before the initiation of Remsima, and in accordance with local recommendations. In this situation, the benefit/risk balance of Remsima therapy should be very carefully considered.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, anti-tuberculosis therapy should be considered before the initiation of Remsima. Use of anti-tuberculosis therapy should also be considered before the initiation of Remsima in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

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

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 Remsima treatment should be carefully considered before initiation or continuation of Remsima therapy.

In patients treated with Remsima, an invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if they develop a serious systematic 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 localized disease, and antigen and antibody testing may be negative in some patients with active infection. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed taking into account both the risk for severe fungal infection and the risks of antifungal therapy.

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

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 Remsima treatment.

Concurrent Administration of TNF-alpha Inhibitor and Anakinra
Concurrent administration of etanercept (another agent that inhibits TNFα) and anakinra (a recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist) has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone.

The safety and efficacy of anakinra used in combination with infliximab has not been established. Therefore, combination of Remsima and anakinra is not recommended.

Concurrent Administration of TNF-alpha Inhibitor and Abatacept
In clinical studies, concurrent administration of TNF-blocking agents and abatacept have been associated with an increased risk of infections including serious infections compared with TNF-blocking agents alone, without increased clinical benefit. Because of the nature of the adverse events seen with the combination of TNF-blocking agents and abatacept therapy, the combination of Remsima 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
When switching from one biologic to another, patients should continue to be monitored, since overlapping biological activity may further increase the risk of infection.

Vaccinations
No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently. Use of live vaccines could result in clinical infections, including disseminated infections.

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

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 FERTILITY, PREGNANCY and LACTATION section).

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 FERTILITY, PREGNANCY and LACTATION section).

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 Remsima and is positive for antibodies against double-stranded DNA, further treatment with Remsima must not be given (see *Adverse Reactions, Anti-nuclear antibodies (ANA)/Double-stranded DNA (dsDNA) antibodies*).

Neurological events

Infliximab and other agents that inhibit TNFα have been associated seizure and 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 Guillian–Barre syndrome (see section 4.4). In patients with pre-existing or recent onset of central nervous system demyelinating disorders, the benefits and risks of Remsima treatment should be carefully considered before initiation of Remsima therapy and should consider discontinuation of Remsima 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. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with long standing, highly active, inflammatory disease, which complicates the 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.

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

Hepatosplenic T-cell Lymphoma

Postmarketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF-blocking agents including infliximab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with or immediately prior to a TNF-blocker. The vast majority of infliximab cases have occurred in patients with Crohn’s disease or ulcerative colitis and most were reported in adolescent or young adult males. Cases of hepatosplenic T-cell lymphoma have also occurred in Crohn's disease patients and ulcerative colitis patients receiving azathioprine or 6-

mercaptopurine who were not treated with infliximab. Before initiating or continuing infliximab therapy in a patient who is receiving an immunosuppressant such as azathioprine or 6-mercaptopurine, the need for continuing the immunosuppressant therapy should be carefully assessed in light of the potential risks of concomitant therapy. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with infliximab cannot be excluded (see section 4.2 and section 4.8).

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 the therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. With current data it is not known if infliximab treatment influences the risk for developing dysplasia or colon cancer (see section 4.8).

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

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

Skin Cancers
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 for all patients, particularly those with risk factors for skin cancer.

Cervical Cancer
A population-based retrospective cohort study using data from Swedish national health registries found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age. A causal relationship between infliximab and cervical cancer cannot be excluded. Periodic screening should continue in women treated with infliximab, including those over 60 years of age

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).

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

Hepatitis B 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 at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating Remsima therapy.

Carriers of HBV who require treatment with Remsima 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 anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, Remsima should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated. Patients should be tested for Hepatitis B Virus (HBV) infection before initiating treatment with immunosuppressants, including infliximab. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Haematologic events
Cases of leukopenia, neutropenia, thombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving infliximab. The causal relationship to infliximab therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with Remsima who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g. persistent fever) while on Remsima. Discontinuation of infliximab therapy should be considered in patients with confirmed significant haematologic abnormalities.

Others
The pharmacokinetics of infliximab in elderly patients has not been studied. The incidence of serious infections in infliximab-treated patients 65 years and older was greater than in those under 65 years of age. In addition, there is a greater incidence of infections in the elderly population in general, therefore, caution should be used in treating the elderly. Studies have not been performed in patients with liver or renal disease (see section 5.2).

There are insufficient preclinical data to draw conclusions on the effects of infliximab on fertility and general reproductive function (see section 5.3).
There is limited safety experience of surgical procedures in infliximab treated patients. The long half-life of infliximab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Remsima should be closely monitored for infections, and appropriate actions should be taken.

There is limited safety experience of infliximab treatment in patients who have undergone arthroplasty.

Treatment of patients with intestinal stricture due to Crohn’s disease is not recommended since the risk/benefit relationship in this patient population has not been established.

4.5 Interactions

Specific drug interaction studies have not been conducted with infliximab.

In rheumatoid arthritis and Crohn’s disease patients, there are indications that concomitant use of methotrexate and other immunomodulators reduces the formation of antibodies against infliximab and increases the plasma concentrations of infliximab. However, the results are uncertain due to limitations in the methods used for serum analyses of infliximab and antibodies against infliximab.

Corticosteroids do not appear to affect the pharmacokinetics of infliximab to a clinically relevant extent.

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

Live Vaccines/Therapeutic Infectious Agents

It is recommended that live vaccines not be given concurrently with infliximab. It is also recommended that live vaccines not be given to infants after in utero exposure to infliximab for 12 months following birth. 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 section 4.4).

It is recommended that therapeutic infectious agents not be given concurrently with infliximab (see 4.4 *Warnings and Precautions, and 4.6 FERTILITY, PREGNANCY and LACTATION sections*).

4.6 FERTILITY, PREGNANCY and LACTATION

Women of childbearing potential

Women of childbearing potential should consider the used 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 5.3 *Preclinical Safety Data* Section).

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 WARNINGS and PRECAUTIONS, and DRUG INTERACTIONS sections). 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 ADVERSE EFFECTS section).

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.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

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 59 and 38 patients for the subcutaneous infliximab group and the intravenous infliximab group, respectively) and active ulcerative colitis patients (evaluated in 38 and 40 patients for the subcutaneous infliximab group and the intravenous infliximab group, respectively) was overall similar to the safety profile of the intravenous formulation.

Adverse Reactions
In clinical studies with intravenous infliximab, adverse drug reactions (ADRs) were observed in approximately 60% of infliximab-treated patients and 40% of placebo-treated patients. The adverse reactions listed in Table 1 and Table 2 are based on experience from clinical trials. Within the organ system classes, adverse reactions are listed under the headings of frequency using the following categories: common (>1/100, <1/10); uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000). Infusion-related reactions were the most common ADRs reported. Infusion-related reactions (dyspnea, urticaria and headache) were the most common cause for discontinuation.

Tabulated list of adverse reactions
Table 1 and Table 2 list 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 of intravenous infliximab

Infections and Infestations Common: Uncommon:	 Viral infection(e.g. influenza, herpes infections) Abscess, cellulitis, moniliasis, sepsis, bacterial infection, tuberculosis, fungal infection, hordeolum

Neoplasms benign, malignant and unspecified Uncommon: Rare:	 Basal cell carcinoma, squamous cell carcinoma Lymphoma
Immune system disorders Common: Uncommon:	 Serum sickness-like reactions Lupus-like syndrome, respiratory tract allergic reactions, anaphylactic reactions
Blood and lymphatic disorders Uncommon:	 Anemia, leukopenia, lymphadenopathy, lymphocytosis, lymphopenia, neutropoenia, thrombocytopenia
Psychiatric disorders Uncommon:	 Depression, confusion, agitation, amnesia, apathy, nervousness, somnolence, insomnia
Nervous system disorders Common: Uncommon: Rare:	 Headache, vertigo/dizziness Exacerbation of demyelinating disease suggestive of multiple sclerosis Meningitis
Eye disorders Uncommon:	 Conjunctivitis, endophthalmitis, keratoconjunctivitis, periorbital oedema
Cardiac disorders Uncommon: Rare:	 Syncope, bradycardia, palpitation, cyanosis, arrhythmia, worsening heart failure Tachycardia
Vascular disorders Common: Uncommon: Rare:	 Flushing Ecchymosis/hematoma, hot flushes, hypertension, hypotension, petechia, thrombophleblitis, vasospasm, peripheral ischaemia Circulatory failure
Respiratory, thoracic and mediastinal disorders Common: Uncommon: Rare:	 Upper respiratory tract infection, lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, sinusitis Epistaxis, bronchospasm, pleurisy, pulmonary oedema Pleural effusion
Gastro-intestinal system Common: Uncommon: Rare:	 Nausea, diarrhea, abdominal pain, dyspepsia Constipation, gastroesophageal reflux, cheilitis, diverticulitis Intestinal perforation, intestinal stenosis, gastrointestinal hemorrhage

Hepatobiliary disorders Common: Rare:	 Abnormal hepatic function, cholecystitis Hepatitis
Skin and subcutaneous tissue disorders Common: Uncommon:	 Rash, pruritus, urticaria, increased sweating, dry skin Fungal dermatitis/ onychomycosis, eczema/ seborrhea, bullous eruption, furunculosis, hyperkeratosis, rosacea, verruca, abnormal skin pigmentation/coloration, alopocia
Musculoskeletal and connective tissue disorders Uncommon:	 Myalgia, arthralgia, back pain
Renal and urinary disorders Uncommon:	 Urinary tract infection, pyelonephritis
Reproductive system and breast disorders Uncommon:	 Vaginitis
General disorders and administration site conditions Common: Uncommon: Rare:	 Fatigue, chest pain, infusion-related reactions, fever Injection site reactions, oedema, pain, chills/rigors, impaired healing Granulomatous lesion
Investigations Common: Uncommon:	 Elevated hepatic transaminases Autoantibodies, complement factor abnormality

Table 2: Adverse Reaction in Post-marketing reports of intravenous infliximab

(common > 1/100, <1/10; uncommon >1/1000, < 1/100; rare >1/10,000, <1/1000, very rare <1/10,000, including isolated reports)

Nervous system disorders Rare: Very rare:	 Central nervous system demyelinating disorders (such as multiple sclerosis and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), neuropathies, numbness, tingling, seizure, cerebrovascular accidents occurring within approximately 24 hours of initiation of infusion Transverse myelitis
Blood and lymphatic system disorders Rare: Very rare:	 Pancytopenia Hemolytic anemia, idiopathic thrombocytopenia purpura, thrombotic thrombocytopenic purpura, agranulocytosis

Neoplasms benign, malignant and unspecified (including cysts and polyps) Rare: Very Rare:	 Hepatosplenic T-cell lymphoma (the vast majority in Crohn's Disease and ulcerative colitis: primarily in adolescent and young adults), lymphoma (including non-Hodgkin's lymphoma and Hodgkin's Disease), leukemia, melanoma, cervical cancer Pediatric malignancy, Merkel cell carcinoma
Immune system disorders Uncommon: Rare:	 Anaphylactic reactions Anaphylactic shock, serum sickness, vasculitis
Cardiac disorders Rare: Very rare:	 Worsening heart failure, new onset heart failure Pericardial effusion
Infections and infestations Rare: Very rare:	 Opportunistic infections (such as tuberculosis, atypical mycobacteria, pneumocystis carinii pneumonia (PCP), pneumocystosis, histoplasmosis, coccidiodomycosis, aspergillosis, listeriosis and candidiasis, cryptococcosis) Salmonellosis, hepatitis B reactivation, protozoal infection, and vaccine breakthrough infection (after *in utero* exposure to infliximab)*
Respiratory, thoracic and mediastinal disorders Rare: Very rare:	 Interstitial lung disease, including pulmonary fibrosis/ interstitial pneumonitis Rapidly progressive interstitial lung disease
Gastrointestinal disorders Rare:	 Pancreatitis
Hepatobiliary disorders Rare: Very rare:	 Hepatitis Hepatocellular damage, jaundice, autoimmune hepatitis, liver failure
Skin and subcutaneous tissue disorders Rare: Very rare:	 Vasculitis (primarily cutaneous) Toxic epidermal necrolysis, Stevens-Johnson-Syndrome, erythema multiforme, psoriasis, including new onset and pustular (primarily palmar/plantar)
General disorders and administration site conditions Common:	 Infusion-related reactions

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

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 a Phase I study conducted in patients with active Crohn's disease and active ulcerative colitis, the safety population consisted of 97 patients in the Remsima subcutaneous group (59 patients with active Crohn's disease and 38 patients with active ulcerative colitis) and 78 patients in the Remsima intravenous group (38 patients with active Crohn's disease and 40 patients with active ulcerative colitis) from Part 1 and Part 2 of the study. For study details, see section 5.1.

The incidence rate of systemic injection reactions (e.g. nausea and dizziness) was 2.3 patients per 100 patient-years in the Remsima subcutaneous group (from Week 6) and there were no systemic injection reactions reported in the Remsima intravenous group who switched to Remsima subcutaneous administration (from Week 30).

The incidence rate of localised injection site reactions (e.g. injection site erythema, pain, pruritus, bruising) was 23.3 patients per 100 patient-years in the Remsima subcutaneous group (from Week 6) and 7.5 patients per 100 patient-years in the Remsima intravenous group who switched to Remsima subcutaneous administration (from Week 30). All 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.

Infusion-Related Reactions in adult patients administered with intravenous infliximab

An infusion-related reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion.

In phase 3 clinical studies, 18% of intravenous infliximab-treated patients compared with 5% of placebo-treated patients experienced an infusion-related reaction. Of intravenous infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period, week 7 through week 54. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period.

Approximately 3% of patients discontinued treatment due to infusion-related reactions, and all patients recovered with or without medical therapy.

In a clinical study of patients with rheumatoid arthritis (ASPIRE), study medication was administered to each patient by infusion over 2 hours for the first 3 study infusions. For patients who did not

experience a serious infusion reaction with the first 3 study infusions, subsequent infusions could be shortened to not less than 40 minutes. Sixty six percent of the patients (686 out of 1040) received at least one shortened infusion of 90 minutes or less and 44% of the patients (454 out of 1040) received at least one shortened infusion of 60 minutes or less. Of the intravenous infliximab-treated patients who received at least one shortened infusion, infusion-related reactions occurred in 15% (74/494) of patients and serious infusion reactions occurred in 0.4% (2/494) of patients. Shortened infusions at doses > 6 mg/kg have not been studied.

In Phase 3 clinical studies, in patients receiving intravenous infliximab with or without concomitant immunomodulator therapy, 13-19% of patients receiving intravenous infliximab at a low infusion rate (≤ 6 mg/kg/2-hr) experienced an infusion-related reaction, compared to 15-16% of patients receiving intravenous infliximab at a high infusion rate (> 6 mg/kg/2-hr or equivalent to >3 mg/kg/1-hr). Of patients receiving intravenous infliximab at a low infusion rate, 0.4%-0.7% experienced a serious infusion-related reaction, compared to 0.4%-0.5% of patients receiving intravenous infliximab at a high infusion rate.

In a clinical study of patients with Crohn's disease (SONIC), infusion-related reactions occurred in 16.6% (27/163) of patients receiving intravenous infliximab monotherapy, 5.0% (9/179) of patients receiving intravenous infliximab in combination with azathioprine, and 5.6% (9/161) of patients receiving azathioprine monotherapy. One patient experienced a serious infusion reaction with intravenous infliximab monotherapy.

In post-marketing surveillance, reports of anaphylactic-like reactions, including laryngeal/pharyngeal edema, severe bronchospasm, and seizure have been associated with intravenous infliximab administration. Cases of transient visual loss occurring during or within 2 hours of intravenous infliximab infusion have been reported. Cerebrovascular accidents, myocardial ischemia/myocardial infarction (some fatal), and arrhythmia occurring within 24 hours of initiation of infusion have also been reported.

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

A clinical study in patients with moderate to severe psoriasis was designed to assess the efficacy and safety of long-term maintenance therapy versus re-treatment with an induction regimen of intravenous infliximab (maximum of four infusions at 0, 2, 6 and 14 weeks) following disease flare. Patients did not receive any concomitant immunosuppressant therapy. In the re-treatment arm, 4% (8/219) of patients experienced a serious infusion reaction versus <1% (1/222) on maintenance therapy. The majority of serious infusion reactions occurred during the second infusion at Week 2. The interval between the last maintenance dose and the first re-induction dose ranged from 35-231 days. Symptoms included, but were not limited to, dyspnea, urticaria, facial oedema, and hypotension. In all cases, intravenous infliximab treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed Hypersensitivity

In a clinical study of 41 patients retreated with intravenous infliximab following a 2 to 4 year period without infliximab treatment, 10 patients experienced undesirable effects manifesting 3 to 12 days following infusion. In 6 of these patients the effects were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash. Some patients also experienced pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and/or headache. No similar set of delayed adverse events has been observed in any other clinical study involving a total of 771 patients receiving 4749 infusions with intervals predominantly of 14 weeks or less, but ranging from 1 to 55 weeks. In ongoing studies and post-marketing reports, these events have been rare and have occurred at intervals of less than 1 year.

In a 1-year trial with repeated infusions 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 antibodies to infliximab and 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 140 of 980 (14%) patients with any immunosuppressant therapy, and in 92 of 383 (24%) patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, 6 of 77 (8%) patients developed antibodies to infliximab. 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 folds 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 (see section 4.4). In psoriasis patients treated with infliximab as a maintenance regimen in the absence of concomitant immunomodulators, approximately 28% developed antibodies to infliximab.

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 and anti-infliximab antibodies had no significant impact on efficacy (determined by clinical response and clinical remission according to CDAI score for Crohn's disease patients or partial Mayo score for ulcerative colitis patients) and the safety profile.

Infections

Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal infections, and other opportunistic infections have been observed in patients receiving infliximab. Some of these infections have been fatal. Opportunistic infections reported in patients on infliximab have included, but are not limited to pneumocystosis, histoplasmosis, cytomegalovirus infection, atypical mycobacterial infections, listeriosis and aspergillosis. 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 intravenous infliximab-treated patients experienced infections compared with 25% of placebo-treated patients.

In RA trials, the incidence of serious infections including pneumonia was higher in intravenous 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 event. Some of the cases have resulted in fatal outcome. Nearly 50% of reported deaths have been associated with

infection. Cases of tuberculosis, sometimes fatal, including miliary tuberculosis and tuberculosis with extrapulmonary location have been reported (see section 4.4).

Malignancies and lymphoproliferative disorders

In clinical studies with intravenous infliximab in which 5706 patients were treated, representing 4990 patient years, 5 cases of lymphomas and 24 non-lymphoma malignancies were detected as compared with no lymphomas and 1 non-lymphoma malignancy in 1600 placebo-treated patients representing 892 patients years.

In long-term safety follow-up of clinical studies with infliximab of up to 5 years, representing 6234 patients-years (3210 patients), 5 cases of lymphoma and 38 cases of non-lymphoma malignancies were reported.

From August 1998 to August 2005, 1909 cases of suspected malignancies have been reported from post marketing, clinical trials and registries (321 in Crohn's disease patients, 1302 in rheumatoid arthritis patient and 286 in patients with other or unknown indication). Among those there were 347 lymphoma cases. During this period, the estimated exposure is 1,909,941 patient years since first exposure (see section 4.4).

In an explanatory clinical trial involving patients with moderate to severe COPD who were either current smoker or ex-smokers, 157 patients were treated with intravenous infliximab at doses similar to those used in RA 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% Cl 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% Cl 0.03%-7.0%]. The majority of the malignancies developed in the lung or head and neck.

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

Heart failure

In a phase II study aimed at evaluating intravenous infliximab in congestive heart failure (CHF), higher incidence of mortality due to worsening of heart failure were seen in patients treated with intravenous infliximab, especially those treated with the higher dose of 10 mg/kg (i.e. twice the maximum approved dose). In this trial, 150 patients with NYHA Class Ⅲ-Ⅳ CHF (left ventricular ejection fraction ≤35%) were treated with 3 infusions of intravenous infliximab 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 38 weeks, 9 of 101 patients treated with intravenous 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 intravenous 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.

Antinuclear Antibodies (ANA)/Anti-Double-Stranded DNA (dsDNA) Antibodies

In clinical studies, approximately half of intravenous infliximab-treated patients who were ANA negative at baseline developed a positive ANA during the trial (compared with approximately one-fifth placebo-treated patients). Anti-dsDNA antibodies developed in approximately 17% of patients treated with intravenous infliximab (compared with 0% of placebo-treated patients). At the last evaluation, 57% intravenous infliximab-treated patients remained anti-dsDNA positive. Clinical signs consistent with a lupus-like syndrome remained uncommon.

Hepatobiliary events

In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving intravenous infliximab without progression to severe hepatic injury. Elevations of ALT 5 x Upper Limit of Normal (ULN) have been observed (see Table 3). Elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving intravenous infliximab than in controls, both when intravenous 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 intravenous infliximab, or modification of concomitant medications.

In post-marketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving intravenous infliximab (see section 4.4)

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

indication	Number of Patients[3]		Median follow-up (wks)[4]		Proportion of patients with increased ALT			
					≥3xULN		≥5xULN	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	infliximab
Rheumatoid arthritis[1]	375	1087	58.1	58.3	3.2%	3.9%	0.8%	0.9%
Crohn's disease[2]	324	1034	53.7	54.0	2.2%	4.9%	0.0%	1.5%
Pediatric Crohn's disease	N/A	139	N/A	53.0	N/A	4.4%	N/A	1.5%
Ulcerative colitis	242	482	30.1	30.8	1.2 %	2.5%	0.4%	0.6%
Pediatric Ulcerative colitis	N/A	60	N/A	49.4	N/A	6.7%	N/A	1.7%
Ankylosing spondylitis	76	275	24.1	101.9	0.0%	9.5%	0.0%	3.6%
Psoriatic arthritis	98	191	18.1	39.1	0.0%	6.8%	0.0%	2.1%
Plaque psoriasis	281	1175	16.1	50.1	0.4%	7.7%	0.0%	3.4%

[1] Placebo patients received methotrexate while infliximab patients received both infliximab and methotrexate.
[2] Placebo patients in the 2 of the 3 Phase III trials in Crohn's disease, ACCENT I and ACCENT II, received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patient who were randomized to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in the ALT analysis. In the Phase IIIb trial in Crohn's disease, SONIC, placebo patients received AZA 2.5 mg/kg/day in addition to placebo infusions.
[3] Number of patients evaluated for ALT.
[4] Median follow-up is based on patients treated.

Special populations

Elderly

In rheumatoid arthritis clinical studies, the incidence of serious infections was greater in intravenous 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 national reporting system.

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. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, tumour necrosis factor alpha (TNFα) inhibitors, ATC code: L04AB02.

Remsima is a subcutaneous formulation of biosimilar medicinal product.

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 was assessed in two multicentre, randomised, double-blind, pivotal trials: 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 were permitted.

The primary endpoints were the reduction of signs and symptoms as assessed by the American College Rheumatology criteria (ACR20 for ATTRACT, landmark ACR-N for ASPIRE), the prevention of structural joint damage, and the improvement in physical function. A reduction in signs and symptoms was defined to be at least a 20% improvement (ACR20) in both tender and swollen joint counts, and in 3 of 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 trial 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, HAQ and total van der Heijde-modified Sharp score) are shown in Table 4. 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 4).

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 4: Effects on ACR20, Structural Joint Damage and Physical Function at week 54

		infliximab[b]	

	Control[a]	3 mg/kg q8wks	3 mg/kg q4wks	10 mg/kg q8wks	10 mg/kg q4wks	All infliximab[b]
Patients with ACR20 response/ patients evaluated(%)[c]	15/88 (17%)	36/86 (42%)	41/86 (48%)	51/87 (59%)	48/81 (59%)	176/340 (52%)
Total score[d] (van der Heijde-modified Sharp score)						
Change from baseline (Mean± SD[C])	7.0±10.3	1.3±6.0	1.6±8.5	0.2±3.6	-0.7±3.8	0.6±5.9
Median[c] (interquartile range)	4.0 (0.5,9.7)	0.5 (-1.5,3.0)	0.1 (-2.5,3.0)	0.5 (-1.5,2.0)	-0.5 (-3.0,1.5)	0.0 (-1.8,2.0)
patients with no deterioration/ patients evaluated (%)[c]	13/64 (20%)	34/71 (48%)	35/71 (49%)	37/77 (48%)	44/66 (67%)	150/285 (53%)
HAQ change from base line over time[e] (patients evaluated)	87	86	85	87	81	339
Mean±SD[C]	0.2±0.3	0.4±0.3	0.5±0.4	0.5±0.5	0.4±0.4	0.4±0.4

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

The ASPIRE trial evaluated responses at 54 weeks in 1004 methotrexate naïve 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 (optimized to 20 mg/wk by week 8) and either placebo, 3 mg/kg or 6 mg/kg infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter. Results from week 54 are shown in Table 5.

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 structure damage was observed at weeks 30 and 54 in the infliximab + methotrexate groups compared to methotrexate alone.

Table 5: 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 randomized	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

Comparative clinical efficacy and safety studies for intravenous Remsima
Efficacy
The pivotal efficacy and safety comparability trial comparing Remsima and the reference product was a randomized, double-blind, multicentre, parallel-group, prospective Phase III study in adult patients with active RA not receiving adequate response with methotrexate alone.

The primary efficacy endpoint (the proportion of patients achieving clinical response according to the ACR20 criteria at Week 30) is summarized for the all-randomized population in Table 6**.**

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

A comparison of the Mean change from baseline for each individual ACR component is presented in Table 7. ACR20/50/70 responses at weeks 14, 30, and 54 are compared between Remsima and the referenced product in Table 8.

Table 6 : Proportion of Patients Achieving Clinical Response According to ACR20 Criteria at Week 30 – Study CT-P13 3.1 in Rheumatoid Arthritis: All-Randomized Population

Treatment group	n/N (%)	Estimate of treatment difference*	95% CI of treatment difference
Remsima	184/302 (60.9)	0.02	-0.06, 0.10
Remicade	178/304 (58.6)		

ACR20=20% improvement according to the ACR criteria, CI=Confidence interval, n=Number of patients with an assessment; N=Number of all patients in this group, P value: logistic regressions analysis
*= $\Delta\%*10^{-2}$ Remsima and Remicade.

Table 7: Mean Change ± SD from Baseline in the ACR Components at Week 54– Study CT-P13 3.1 (All-Randomized Population)

ACR component	n/N (%)		Remsima	Remicade
	Remsima	Remicade		
Tender joints	235/302 (77.8)	226/304 (74.3)	-16.7±12.08	-15.4±12.30
Swollen joints	235/302 (77.8)	226/304 (74.3)	-12.3±8.69	-12.0±8.85
VAS scores for the patient assessment of pain	235/302 (77.8)	226/304 (74.3)	-30.6±23.86	-28.7±26.89
VAS scores for the patient global assessment of disease activity	234/302 (84.4)	226/304 (74.3)	-30.6±24.41	-26.8±27.76
VAS scores for the physician global assessment of disease activity	235/302 (77.8)	226/304 (74.3)	-37.3±21.52	-35.9±22.51
Scores for the health assessment questionnaire	235/302 (77.8)	226/304 (74.3)	-0.61±0.61	-0.53±0.60
CRP (mg/dl)	233/302 (77.2)	224/304 (73.9)	-0.68±2.18	-0.64±2.63
ESR (mm/h)	233/302 (77.2)	225/304 (74.0)	-12.0±22.00	-15.1±21.71

ACR=American College of Rheumatology; n=Number of patients for this evaluation; N=Number of all patients in this group; SD=Standard deviation

Table 8 :Proportion of Patients Achieving Clinical Response According to ACR20 at Weeks 14, 30 and 54, as well as ACR50, and ACR70 Criteria at Weeks 14, 30 and 54 (Exact Binomial method) – Study CT-P13 3.1 (All-Randomized Population)

ACR scores	n/N (%)		Estimate of treatment difference [1]	95% CI of treatment difference
	Remsima	Remicade		
ACR20 at Week 14	192/302 (63.6)	175/304 (57.6)	0.06	-0.02, 0.14
ACR20 at Week 30	184/302 (60.9)	178/304 (58.6)	0.02	-0.06, 0.10
ACR20 at Week 54	172/302 (57.0)	158/304 (52.0)	0.05	-0.03, 0.13
ACR50 at Week 14	100/302 (33.1)	91/304 (29.9)	0.03	-0.04, 0.11
ACR50 at Week 30	107/302 (35.4)	103/304 (33.9)	0.02	-0.06, 0.09
ACR50 at Week 54	100/302 (33.1)	96/304 (31.6)	0.02	-0.06, 0.09
ACR70 at Week 14	42/302 (13.9)	37/304 (12.2)	0.02	-0.04, 0.07
ACR70 at Week 30	50/302 (16.6)	47/304 (15.5)	0.01	-0.05, 0.07
ACR70 at Week 54	49/302 (16.2)	46/304 (15.1)	0.01	-0.05, 0.07

ACR20=20% improvement according to the ACR criteria; ACR50=50% improvement according to the ACR criteria; ACR70=70% improvement according to the ACR criteria; CI=Confidence interval; n=Number of patients with an assessment; N=Number of all patients in this group
[1] Estimate of the difference in proportions between the two treatment groups (Remsima – Remicade) using the exact binomial test.

Safety
In Study CT-P13 3.1, TEAEs occurred in 212 (70.2%) patients treated with Remsima compared to 211 (70.3%) patients treated with Remicade. The most frequently reported TEAEs were latent tuberculosis (8.9% vs. 8.3% patients, respectively), anemia (3.3% vs. 4.0%), nasopharyngitis (7.9% vs. 5.7%), hypertension (5.0% vs. 3.3%), urinary tract infection (6.0% vs. 7.0%), rheumatoid arthritis (5.0% vs. 3.7%), upper respiratory tract infection (8.9% vs. 5.3%), alanine aminotransferase (ALT) increased (5.0% vs. 5.7%), headache (4.3% vs. 5.3%), and bronchitis (4.3% vs. 5.7%). TEAEs due to infusion-related reactions were reported for 10 (3.3%) patients and 11 (3.7%) patients in the Remsima and Remicade treatment groups, respectively. Infusion-related reactions that were considered serious occurred in 5 (1.7%) Remsima patients and in 4 (1.3%) Remicade patients.

The safety analyses included all patients who received at least one (full or partial) dose of either of the study treatments during any dosing period. The safety population for each treatment arm is as follows: Remsima N=302, Remicade N=300.

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 Week 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 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 to at each time point until Week 54 in each treatment arm (see Table 9 and Table 10 respectively)

Table 9: Mean (SD) Actual Values of DAS28 (CRP and ESR)

	DAS28 (CRP)		DAS28 (ESR)	
	Remsima IV 3 mg/kg[b]	Remsima SC 120 mg	Remsima IV 3 mg/kg[b]	Remsima SC 120 mg
Visit	(N=174)	(N=165)	(N=174)	(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)
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 10: Proportions of Patients Achieving Clinical Response According to the ACR Criteria

	ACR20		ACR50		ACR70	
	Remsima IV 3 mg/kg[a]	Remsima SC 120 mg	Remsima IV 3 mg/kg[a]	Remsima SC 120 mg	Remsima IV 3 mg/kg[a]	Remsima SC 120 mg
Visit	(N=174)	(N=165)	(N=174)	(N=165)	(N=174)	(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 and efficacy (including DAS28 and ACR20 response) in rheumatoid arthritis patients treated with Remsima 120 mg given subcutaneously every 2 weeks 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 was assessed in 108 patients with active Crohn′s disease (Crohn′s Disease Activity Index (CDAI) ≥220≤400) in a randomized, double-blinded, placebo-controlled, close-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 medications.

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 Crohn's disease medications 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 a singles dose of study medication, 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
The efficacy of repeated infusions with infliximab was studied in a 1- year clinical study.

A total of 573 patients with active Crohn's disease (DCAI ≥220≤ 400) received a single infusion of 5 mg/kg at week0. Sixty-eight of these patients (12%) belonged to the population defined in the indication (see *Indications).* Three hundred and thirty-five patients (58%) responding to the 5 mg/kg infusion at week 2 were randomized to one of three treatment groups; a placebo maintenance group, 5 mg/kg maintenance group and 10 mg/kg maintenance group, receiving repeated infusions at week 2, 6, and every eight weeks.

At week 30, a significantly greater proportion of patients in the combined infliximab maintenance treatment group (42%) achieved clinical remission, compared with patients in the placebo maintenance group (21%). Median time to loss of response was 46 weeks in the combined infliximab maintenance treatment group vs. 19 weeks in the placebo maintenance group ($p<0.001$). Similar results were obtained in the subgroup analyses of the population defined in the indication (see *Indications*).

Improvements in quality of life measures were seen for both the IBDQ and SF-36 scores in the infliximab maintenance groups compared with the placebo maintenance group at week 30 ($p< 0.001$).

Infliximab with or without AZA was assessed in a randomized, 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 randomized 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 11. 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 11: Percent of patients achieving corticosteroid-free clinical remission at Week 26, SONIC

	AZA	Infliximab	Infliximab + AZA

	Monotherapy	Monotherapy	Combination Therapy
Week 26 All randomized 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 Crohn's Disease
The efficacy was assessed in a randomized, double-blinded, placebo-controlled study in 94 patients with fistulising Crohn's disease who had fistulae that were of at least 3 months' duration. Thirty-one of these patients were treated with infliximab 5 mg/kg. Approximately 93% of the patients had previously received antibiotic or immunosuppressive therapy.

Concurrent use of stable doses of conventional therapies was permitted, and 83% of patients continued to receive at least one of these medications. 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 medication 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 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 Crohn's Disease
The efficacy of repeated infusion with infliximab in patients with fistulising Crohn's disease was studied in a 1-year clinical study. A total of 306 patients received 3 doses of infliximab 5 mg/kg at week 0, 2, and 6. At baseline, 87% of the patients had perianal fistulae, 14% had abdominal fistulae, 9% had rectovaginal fistulae. The median CDAI score was 180. At week 14, 282 patients were assessed for clinical response and randomised to receive either placebo or 5 mg/kg infliximab every 8 weeks through week 46.

Week-14 responders (195/282) were analyzed for the primary endpoint, which was time from randomisation to loss of response (see Table 12). Corticosteroid tapering was permitted after week 6.

Table 12: 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.

Comparative clinical efficacy and safety studies for intravenous Remsima
Efficacy
The primary objective of CT-P13 3.4 was to demonstrate that Remsima is noninferior to Remicade at Week 6, in terms of efficacy, as determined by the crohn's disease activity index (CDAI)-70 response rate.
The primary efficacy endpoint (the proportion of patients achieving clinical response according to the CDAI-70 criteria at Week 6) is summarized for the all-randomized population in Table 13.

Table 13: Proportion of Patients Achieving CDAI–70 response at Week 6 – Study CT-P13 3.4 in active CD patients: All-Randomized Population

Treatment group	n/N (%)	Estimate of treatment difference	Lower bound of 95% CI of treatment difference
Remsima	77/111 (69.4)	-4.9	-17.0
Remicade	81/109 (74.3)		

Remsima= Remsima – Remsima and Remsima –Remicade treatment group; Remicade = Remicade – Remicade and Remicade –Remsima treatment group
CDAI=Crohn's disease activity index, CI=Confidence interval, n=the number of patients with a response; N=Number of all patients in each group

The proportion of patients achieving CDAI-70 response in the Remsima treatment group was noninferior to that in the Remicade treatment group in the all randomized population (77 [69.4%] patients and 81 [74.3%] patients in the Remsima and Remicade treatment groups, respectively). The treatment difference estimates using exact binomial method were -4.9% (lower bound of 95% CI, -17.0) in the all randomized population.

The proportion of patients achieving clinical remission, and CDAI-100 responses at weeks 6, 14, 30, and 54, as well as CDAI-70 response at Week 14, 30, and 54 are compared between Remsima and the referenced product are summarized for the all-randomized population in Table 14 and Table 15.

Table 14: Proportion of Patients Achieving Clinical Response According to CDAI-100 at Weeks 6, 14, 30 and 54, as well as CDAI-70 at Weeks 14, 30 and 54 – Study CT-P13 3.4: All-Randomized Population

	n/N (%)			
	Remsima – Remsima	Remsima – Remicade	Remicade – Remicade	Remicade – Remsima
CDAI-70 at Week 14	96/111 (86.5)		96/109 (88.1)	
CDAI-70 at Week 30	85/111 (76.6)		82/109 (75.2)	
CDAI-70 at Week 54	44/56 (78.6)	39/55 (70.9)	38/54 (70.4)	42/55 (76.4)
CDAI-100 at Week 6	67/111 (60.4)		70/109 (64.2)	
CDAI-100 at Week 14	78/111 (70.3)		83/109 (76.1)	

	n/N (%)			
	Remsima – Remsima	**Remsima – Remicade**	**Remicade – Remicade**	**Remicade – Remsima**
CDAI-100 at Week 30	80/111 (72.1)		80/109 (73.4)	
CDAI-100 at Week 54	43/56 (76.8)	38/55 (69.1)	34/54 (63.0)	41/55 (74.5)

CDAI=Crohn's disease activity index, CI=Confidence interval, n=the number of patients with a response; N=Number of all patients in this group.

Table 15: Proportion of Patients Achieving clinical remission at Weeks 6, 14, 30 and 54 – Study CT-P13 3.4: All-Randomized Population

	n/N (%)			
	Remsima – Remsima	**Remsima – Remicade**	**Remicade – Remicade**	**Remicade – Remsima**
Remission at Week 6	47/111 (42.3)		49/109 (45.0)	
Remission at Week 14	59/111 (53.2)		60/109 (55.0)	
Remission at Week 30	61/111 (55.0)		62/109 (56.9)	
Remission at Week 54	35/56 (62.5)	32/55 (58.2)	29/54 (53.7)	33/55 (60.0)

CDAI=Crohn's disease activity index, CI=Confidence interval, n=the number of patients with a response; N=Number of all patients in this group
Clinical Remission is defined as an absolute CDAI score of less than 150 points.

Safety
In CT-P13 3.4 (Crohn's disease) study, the proportion of patients who experienced at least 1 TEAE was similar between the 4 treatment groups (36 [64.3%], 34[68.5%], 37[68.5%], and 40[72.7%] in the C-C, C-R, R-R, and R-C treatment groups respectively). The most frequently reported TEAEs were abdominal pain (5.4%, 16.4%, 9.3% and 7.3%), anemia (8.9%, 9.1%, 9.3% and 7.3%), infusion-related reaction (Before drug switching, 7.2% and 8.3% in Remsima(CT-P13) and Remicade treatment groups. Over 1 year, 14.3%, 3.6%, 9.3% and 7.3% in C-C, C-R, R-R and R-C treatment groups respectively), and arthralgia (5.4%, 1.8%, 7.4% and 7.3%). The majority of TEAEs were considered by the investigator to be unrelated to the study drug. Treatment-emergent AEs considered by the investigator to be related to study drug were reported for 17 (30.4%), 12 (21.8%), 17 (31.5%), and 17 (30.9%) patients in the C-C, C-R, R-R, and R-C treatment groups, respectively. Treatment-emergent AEs leading to permanent discontinuation of study drug were reported for 3 (5.4%), 3 (5.5%), 3 (5.6%), and 3 (5.5%) patient in the C-C, C-R, R-R, and R-C treatment groups, respectively. No deaths or malignancy were reported during the study. Overall, Remsima was well tolerated and the safety profile of Remsima was similar to that of Remicade

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).

Adult ulcerative colitis

Intravenous formulation

The safety and efficacy of infliximab were assessed in two (ACT 1 and ACT 2) randomized, 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 agent were permitted. In both studies, patients were randomized 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 16: Effect on clinical response, clinical remission and mucosal healing at Weeks 8 and 30.

Combined data from ACT 1 & 2

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg	Combined
Subject randomized	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 trial.

At 54 weeks, 44.9% of patients in the combined infliximab treatment group were in clinical response compared to 19.8% in the placebo treatment group ($p<0.001$). Clinical remission and mucosal healing occurred in greater proportion of patients in the combined infliximab treatment group compared to the placebo treatment group at week 54 (34.5% vs. 16.5%, $p<0.001$ and 46.1% vs. 18.2%, $p<0.001$, respectively). The proportion of patients in sustained response and sustained remission at week 54 were greater in the combined infliximab treatment group than in placebo treatment group (37.9% vs. 14.0%, $p<0.001$; and 20.2% vs. 6.6%, $p<0.001$, respectively).

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

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

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

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 were studied in a double-blind, placebo-controlled investigator initiated, multicenter study evaluating infliximab in 70 patients with active ankylosing spondylitis (disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score > 4] and pain [NRS score >4]). During the 3-month double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6 (35 patients in each group). Starting at week 12, placebo patients were switched to infliximab and all patients subsequently received 5 mg/kg infliximab every 6 weeks up to week 54.

Treatment with infliximab resulted in improvement in signs and symptoms, as assessed by the BASDAI, with 57% of infliximab treated patients achieving at least 50% reduction from baseline in BASDAI score (mean baseline score was 6.5 in the infliximab group and 6.3 in the placebo group, compared with 9% of placebo patients ($p<0.01$). Improvement was observed at week 2 and was maintained through week 54. Physical function and quality of life (SF36) were improved similarly. In the trial, efficacy was not shown in HLA-B27 negative patients (n=7).

Comparative clinical efficacy and safety studies for intravenous Remsima
Efficacy
A randomized, double-blind, multicenter, parallel-group, study designed to assess PK comparability, also compared the efficacy and safety of Remsima to Remicade in patients with active AS. Investigations of efficacy and safety were secondary to the primary pharmacokinetic endpoints. The study was unblinded at Week 30 for reporting; however, the study remained blinded to the investigators and patients until the end of the study (54 weeks) to reduce bias. No clinically meaningful differences were suggested when the proportions of patients achieving clinical response, according to the ASAS20 and ASAS40 criteria at weeks 14, 30 and 54 were compared between treatment groups. See Table 17.

Table 17: Proportion of Patients Achieving Clinical Response According to the ASAS20 and ASAS40 Criteria (Weeks 14, 30, and 54): All-Randomized Population

– Study CT-P13 1.1 in Ankylosing Spondylitis

ASAS scores	n/N (%)		Estimate of treatment difference	95% CI of treatment difference
	Remsima	Remicade		
ASAS20 at Week 14	72/125 (57.6)	79/125 (63.2)	-0.06	(-0.18, 0.07)
ASAS20 at Week 30	79/125 (63.2)	84/125 (67.2)	-0.04	(-0.16, 0.08)
ASAS20 at Week 54	71/125 (56.8)	75/125 (60.0)	-0.03	(-0.15, 0.09)
ASAS40 at Week 14	48/125 (38.4)	56/125 (44.8)	-0.06	(-0.19, 0.06)
ASAS40 at Week 30	58/125 (46.4)	55/125 (44.0)	0.02	(-0.10, 0.15)
ASAS40 at Week 54	58/125 (46.4)	53/125 (42.4)	0.04	(-0.08, 0.16)

ASAS: Ankylosing Spondylitis Assessment
Note: n = the number of subjects with the event.
N = the number of subjects with an assessment.
(%) = n/N'*100.
[1] Estimate of the difference in proportions between the two treatment groups (Remsima- Remicade) using the exact binomial test.

Safety
In CT-P13 1.1 (ankylosing spondylitis) study, treatment emergent adverse events (TEAEs) occurred in 93 (72.7%) patients treated with Remsima compared to 82 (67.2%) patients treated with Remicade. The most frequently reported TEAEs were neutropenia (3.1% vs 4.1% patients, respectively), diarrhea (4.7% vs 0.8%), influenza (1.6%, 4.9%), latent tuberculosis (6.3% vs 4.1%), nasopharyngitis (9.4 vs 8.2), pharyngitis (3.1% vs 5.7%), upper respiratory tract infection (7.8% vs 10.7%), urinary tract infection (6.3% vs 0.8%), alanine aminotransferase (ALT) increased (14.8% vs 15.6%), AST (12.5% vs 10.7%), Blood creatine phosphokinase (CPK) increased (6.3% vs 4.1%), gamma glutamyltransferase (GGT) increased (3.1% vs 5.7%), headache (7.8% vs 5.7%), rash (0.8% vs 4.1%).

The safety analyses included all patients who received at least one (full or partial) dose of either of the study treatments during any dosing period. The safety population for each treatment arm is as follows: Remsima N=128, Remicade N=122.

Adult psoriatic arthritis

Intravenous formulation

Efficacy

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

In the second trial (IMPACT 2), efficacy and safety of infliximab were studied in 200 patients with active psoriatic arthritis (≥5 swollen joints and ≥5 tender joints). 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 and shown in Table 18 below:

Table 18: Effects on ACR and PASI in IMPACT and IMPACT 2

	IMPACT			**IMPACT 2***		
	Placebo (Week 16)	**Infliximab (Week16)**	**Infliximab (Week 98)**	**Placebo (Week 24)**	**Infliximab (Week 24)**	**Infliximab (Week 54)**
Patients randomized	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.

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

Clinical Efficacy
Efficacy
The efficacy of infliximab was assessed in two multicenter, randomized, 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). Prior therapy with PUVA, methotrexate, cyclosporine, or acitretin had been received by 71.4% of patients, although they were not necessarily therapy resistant. Key results are presented in Table 19. 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 19: Summary of PASI response, PGA response and percent of patients with all nails cleared at Week 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%)

a: p<0.001, for each infliximab treatment group vs. control
b: n=292
c: Analaysis 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).

Comparative Immunogenicity data for intravenous and subcutaneous Remsima (RA, CD, and UC)
In both Studies CT-P13 3.5 Part 2 and CT-P13 1.6 Part 2, samples that were positive for ADA were tested for neutralizing capacity.
A summary of the immunogenicity testing (ADA and NAb results) is presented in Table 20 for Study CT-P13 3.5 Part 2 and Table 21 and Table 22 for Study CT-P13 1.6 Part 2.

Table 20: Summary of Immunogenicity Testing: Safety Population - Study CT-P13 3.5 Part 2 in Patients with Rheumatoid Arthritis

	Remsima IV 3 mg/kg (N=175) n (%)	**Remsima SC 120 mg (N=168) n (%)**
Week 0 (Pre-dose)		
ADA Positive	8 (4.6)	5 (3.0)
NAb Positive (as % of ADA positive)	2 (25.0)	0
Week 6		
ADA Positive	18 (10.3)	21 (12.5)
NAb Positive (as % of ADA positive)	12 (66.7)	15 (71.4)
Week 14		
ADA Positive	70 (40.0)	36 (21.4)
NAb Positive (% of as ADA positive)	56 (80.0)	31 (86.1)
Week 22		
ADA Positive	104 (59.4)	53 (31.5)
NAb Positive (% of as ADA positive)	69 (66.3)	37 (69.8)
Week 30		
ADA Positive	107 (61.1)	49 (29.2)
NAb Positive (% of as ADA positive)	65 (60.7)	34 (69.4)
Week 38		
ADA Positive	68 (38.9)	51 (30.4)

	Remsima IV 3 mg/kg (N=175) n (%)	Remsima SC 120 mg (N=168) n (%)
NAb Positive (% of as ADA positive)	55 (80.9)	40 (78.4)
Week 46		
ADA Positive	60 (34.3)	44 (26.2)
NAb Positive (% of as ADA positive)	50 (83.3)	34 (77.3)
Week 54		
ADA Positive	64 (36.6)	48 (28.6)
NAb Positive (% of as ADA positive)	43 (67.2)	36 (75.0)

Note: The immunogenicity ADA test involved both a screening and confirmatory assay to confirm positive results. Samples that were positive in the screening assay were spiked with excess drug to determine if they are a true positive. Percentages for the Neutralizing antibody result are based on the number of positive ADA results at that visit.
ADA: Anti-drug antibody, N: Number of all patients in this group, NAb: Neutralizing antibody

Table 21: Summary of Immunogenicity Testing - Safety Population - Study CT-P13 1.6 Part 2 in Patients with Crohn's Disease

	Remsima IV 5 mg/kg (N=25) n (%)	Remsima SC 120/ 240 mg (N=28) n (%)
Week 0 (Pre-dose)		
ADA Positive	2 (8.0)	0 (0)
NAb Positive (as % of ADA positive)	0 (0)	0 (0)
Week 6		
ADA Positive	3 (12.0)	2 (7.1)
NAb Positive (as % of ADA positive)	1 (33.3)	0 (0)
Week 14		
ADA Positive	5 (20.0)	6 (21.4)
NAb Positive (% of as ADA positive)	4 (80.0)	3 (50.0)
Week 22		
ADA Positive	6 (24.0)	8 (28.6)
NAb Positive (% of as ADA positive)	1 (16.7)	0
Week 30		
ADA Positive	8 (32.0)	10 (35.7)
NAb Positive (% of as ADA positive)	6 (75.0)	0
Week 38		
ADA Positive	6 (24.0)	12 (42.9)
NAb Positive (% of as ADA positive)	1 (16.7)	2 (16.7)
Week 46		
ADA Positive	6 (24.0)	13 (46.4)
NAb Positive (% of as ADA positive)	1 (16.7)	1 (7.7)
Week 54		
ADA Positive	5 (20.0)	14 (50.0)
NAb Positive (% of as ADA positive)	1 (20.0)	1 (7.1)

Note: The immunogenicity ADA test involved both a screening and confirmatory assay to confirm positive results. Samples that were positive in the screening assay were spiked with excess drug to determine if they are a true positive. Percentages for the Neutralizing antibody result are based on the number of positive ADA results at that visit.
ADA: Anti-drug antibody, N: Number of all patients in this group, NAb: Neutralizing antibody

Table 22: Summary of Immunogenicity Testing - Safety Population - Study CT-P13 1.6 Part 2 in Patients with Ulcerative Colitis

	Remsima IV 5 mg/kg (N=40) n (%)	Remsima SC 120/240 mg (N=38) n (%)
Week 0 (Pre-dose)		
ADA Positive	0 (0)	0 (0)
NAb Positive (as % of ADA positive)	0 (0)	0 (0)
Week 6		
ADA Positive	4 (10.0)	1 (2.6)
NAb Positive (as % of ADA positive)	0 (0)	1 (100.0)
Week 14		
ADA Positive	14 (35.0)	8 (21.1)
NAb Positive (% of as ADA positive)	5 (35.7)	4 (50.0)
Week 22		
ADA Positive	26 (65.0)	13 (34.2)
NAb Positive (% of as ADA positive)	11 (42.3)	4 (30.8)
Week 30		
ADA Positive	27 (67.5)	15 (39.5)
NAb Positive (% of as ADA positive)	13 (48.1)	2 (13.3)
Week 38		
ADA Positive	21 (52.5)	17 (44.7)
NAb Positive (% of as ADA positive)	9 (42.9)	2 (11.8)
Week 46		
ADA Positive	17 (42.5)	19 (50.0)
NAb Positive (% of as ADA positive)	8 (47.1)	4 (21.1)
Week 54		
ADA Positive	20 (50.0)	17 (44.7)
NAb Positive (% of as ADA positive)	8 (40.0)	3 (17.6)

Note: The immunogenicity ADA test involved both a screening and confirmatory assay to confirm positive results. Samples that were positive in the screening assay were spiked with excess drug to determine if they are a true positive. Percentages for the Neutralizing antibody result are based on the number of positive ADA results at that visit.
ADA: Anti-drug antibody, N: Number of all patients in this group, NAb: Neutralizing antibody

5.2 Pharmacokinetic properties

Primary PK endpoint Result for subcutaneous Remsima

The result for the primary endpoint of CT-P13 3.5 Part 2 and 1.6 Part 2 are summarised below in Table 23 and Table 24, respectively.

CT-P13 3.5 Part 2 (RA) PK result
124/152 (81.6%) patients in CT-P13 SC Remsima120 mg treatment arm achieved observed C_{trough} greater than the minimum therapeutic efficacy concentration level of infliximab (1 μg/mL) at Week 28.

Table 23: Proportion of Patients with Observed C_{trough} > 1 μg/mL for Each Treatment Arm in Study CT- P13 3.5 Part 2: PK Population

Visit	Week 22	Week 24	Week 26	Week 28
CT-P13 SC 120 mg, n (%)	33/42 (78.6)	35/41 (85.4)	35/40 (87.5)	124/152 (81.6)

CT-P13 IV 3 mg/kg, n (%)	44/156 (28.2)	N/A	N/A	N/A

Note: Patients who reported observed C_{trough} greater than 1 µg/mL (actual concentration before the next administration) between Week 22 and Week 30 were included. The denominator used for percentage calculation was the number of patients in PK population who have observed C_{trough} values at each time point.
C_{trough}: T_{rough} serum concentration at steady state, IV: Intravenous, N/A: Not applicable, SC: Subcutaneous

CT-P13 1.6 Part 2 (IBD) PK result

The primary endpoint of Study CT-P13 1.6 Part 2 was $C_{trough,week22}$(pre-dose level at Week 22). A statistical analysis of covariance model (ANCOVA) for patients who received all doses (full) of study drug up to Week 22 in the PK population was used to conduct statistical comparison of $C_{trough,week22}$ between the CT-P13 IV 5 mg/kg and the CT-P13 SC 120/240 mg arms, and the results are shown below in Table 24. The ratio of geometric LS means of $C_{trough,week22}$ for the CT-P13 IV arm and the CT-P13 SC arm was 1154.17%, and the lower bound of 90% CI of the ratio was 786.37%, well above the pre- defined non-inferiority margin of 80%. The ANCOVA result demonstrated that $C_{trough,week\ 22}$ in the CT-P13 SC arm was non-inferior to $C_{trough,week22}$ in the CT-P13 IV arm.

Table 24: Analysis of Covariance Model (ANCOVA) of Observed $C_{trough,\ week22}$ in Study CT-P13 1.6 Part 2: PK Population

Arm	n	Geometric LS Mean (µg/mL)	Ration (%) of Geometric LS means	90% CI of Ration (%)
CT-P13 IV 5mg/kg	57	1.8181	1154.17	786.37 – 1694.00
CT-P13 SC 120/240mg	59	20.9844		

ANCOVA was conducted considering treatment as fixed effect and current use of treatment with Azathioprine or 6-mercaptopurine or Methotrexate (used or not used), disease (CD or UC), clinical response at Week 6 (responder or non-responder by CDAI-70 for CD or partial Mayo score for UC), and body weight at Week 6 (< 80 kg or ≥ 80 kg) as covariates. The $C_{trough,\ week22}$ (pre-dose level at Week 22) was natural log transformed prior to analysis. The geometric LS means, ratio of geometric LS means and the corresponding 90% CI were obtained by back transforming the LS means, difference in the LS means and the corresponding 90% CI from the ANCOVA based on the natural log transformed values of $C_{trough,\ week22}$. Patients who received all doses (full) of study drug up to Week 22 (prior to Week 22) in the PK Population were included in this summary.
ANCOVA: Analysis of covariance, CD: Crohn's disease, CDAI-70: decrease in CDAI score of 70 points or more from the baseline value, CI: Confidence interval, $C_{trough,\ week22}$: pre-dose at week 22, IV: Intravenous, LS: Least squares, PK: Pharmacokinetics, SC: Subcutaneous, UC: ulcerative colitis

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 58% (95% CI: 54% - 62%).

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 approximately 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.

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

30 months

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze. Keep the medicinal product in its outer carton in order to protect from light.

6.5 Nature and contents of container

Remsima 120 mg solution for subcutaneous injection in a pre-filled syringe
Remsima 120 mg solution for subcutaneous injection in single-use pre-filled syringe (type I glass) with a plunger stopper (flurotec-coated elastomer) and needle with a rigid needle shield.

Packs of:
- 1 prefilled syringe (1 mL sterile solution) with 2 alcohol pads.
- 2 prefilled syringes (1 mL sterile solution) with 2 alcohol pads.

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

Packs of:
- 1 prefilled syringe with automatic needle guard (1 mL sterile solution) with 2 alcohol pads.
- 2 prefilled syringes with automatic needle guard (1 mL sterile solution) with 2 alcohol pads.

Remsima 120 mg solution for subcutaneous injection in pre-filled pen

Remsima 120 mg solution for subcutaneous 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.

6.6 Special precautions for disposal and other handling

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 syringe / pre-filled syringe with automatic needle guard/ 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

CELLTRION HEALTHCARE SINGAPORE
PRIVATE LIMITED

65 CHULIA STREET
#41-02 OCBC Centre,
Singapore (049513)

8 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 June 2023