SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

REMSIMA 100 mg/vial, powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg infliximab*. After reconstitution, each ml contains 10 mg infliximab.

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

Contains sugar:
Each vial contains 500 mg sucrose. After reconstitution, each ml contains 50 mg sucrose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

White lyophilised powder (powder for concentrate for solution for infusion).
Once reconstituted, the solution should be colourless to light yellow and opalescent (see section 6.6).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

In combination with methotrexate, **REMSIMA** is indicated for:

- reduction of signs and symptoms
- prevention of structural joint damage (erosions and joint space narrowing)
- improvement in physical function.

Ankylosing spondylitis

In patients with active disease, **REMSIMA** is indicated for:

- reduction of signs and symptoms
- improvement in physical function.

Psoriatic arthritis

In patients with psoriatic arthritis when the response to disease modifying or non-steroidal anti-inflammatory drugs has been inadequate**, REMSIMA** is indicated for:

- reduction of signs and symptoms of psoriatic arthritis
- induction of major clinical response in active psoriatic arthritis
- inhibition of progression of structural damage of active psoriatic arthritis
- improvement in psoriasis
- improvement of dactylitis and enthesopathy
- improvement in physical function
- improvement in quality of life

REMSIMA can be used with or without methotrexate.

Psoriasis

In the treatment of patients with moderate psoriasis for whom phototherapy is inadequate or inappropriate and adult patients with severe plaque psoriasis who are candidates for systemic therapy, **REMSIMA** is indicated for:

- reduction of signs and symptoms
- improvement in quality of life.

Adult and paediatric (children 6 to 17 years) Crohn's disease
In the treatment of moderate to severe Crohn's disease, **REMSIMA** is indicated for:
- reduction of signs and symptoms
- induction and the maintenance of clinical remission
- induction of mucosal healing
- improvement in quality of life

REMSIMA therapy enables patients to reduce or eliminate the use of corticosteroids.

Fistulising Crohn's disease
In patients with fistulising Crohn's disease, **REMSIMA** is indicated for:
- reduction in the number of draining enterocutaneous and rectovaginal fistulae and the maintenance of fistula closure
- reduction of signs and symptoms
- improvement in quality of life.

Adult and paediatric (children 6 to 17 years) ulcerative colitis
In patients with active ulcerative colitis who have had an inadequate response to conventional therapy, **REMSIMA** is indicated for:
- reduction of signs and symptoms
- induction of mucosal healing
- induction and maintenance of clinical remission
- improvement in quality of life
- reduction or elimination of administration of corticosteroids
- reduction of ulcerative colitis-related hospitalisation.

4.2 Posology and method of administration
For recommended infusion duration for patients for each of the indications described below, see **Method of administration** below.

REMSIMA treatment is to be administered under the supervision of specialised medical practitioners who are experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or inflammatory bowel disease.

REMSIMA should be administered intravenously. Patients treated with **REMSIMA** should be given the patient information leaflet and the special alert card.

During **REMSIMA** treatment, other concomitant therapies, e.g. corticosteroids and immunosuppressants should be optimised.

Posology
Rheumatoid arthritis
Initially a 3 mg/kg intravenous infusion (see **Method of administration** below) followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the initial infusion, then every 8 weeks thereafter. **REMSIMA** should be given in combination with methotrexate. Continued therapy should be reconsidered carefully in patients who do not show evidence of an adequate response within the first 8 weeks of treatment or after dose adjustment.

Ankylosing spondylitis
Initially a 5 mg/kg intravenous infusion (see **Method of administration** below), followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the initial infusion, then every 6 to 8 weeks thereafter. If a patient does not respond within 6 weeks (i.e. after 2 doses), additional treatment with **REMSIMA** should not be given.

Psoriatic arthritis
Initially a 5 mg/kg intravenous infusion (see **Method of administration** below), followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the initial infusion, then every 8 weeks thereafter.

Psoriasis
Initially a 5 mg/kg intravenous infusion (see **Method of administration** below), followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the initial infusion, then every 8 weeks thereafter. If a patient does not respond after 14 weeks, additional treatment should not be given.

Moderate to severe Crohn's disease in adults
For optimal long-term symptom control, 5 mg/kg single intravenous infusion (see **Method of administration** below) as an induction regimen at 0,2 and 6 weeks, followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter. For patients who do not have a complete response during maintenance treatment, consideration may be given to adjusting the dose up to 10 mg/kg.

Alternatively, an initial 5 mg/kg intravenous infusion may be followed by repeat infusions of 5 mg/kg when signs and symptoms of the disease recur; however, data on dosing intervals beyond 16 weeks is limited. There are insufficient safety and efficacy data for the use of **REMSIMA** beyond the recommended duration (see section 4.1). Continued therapy should be carefully considered in patients who show no evidence of therapeutic benefit after dose adjustment.

Paediatric Crohn's disease
Initially a 5 mg/kg intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the initial infusion, then every 8 weeks thereafter. For patients who do not have a complete response, consideration may be given to adjust the dose up to 10 mg/kg. **REMSIMA** must be administered with concomitant immunomodulators, including 6-mercaptopurine (6-MP), azathioprine (AZA) or methotrexate (MTX).

Fistulising Crohn's disease in adults
Initially a 5 mg/kg intravenous infusion (see **Method of administration** below), followed by additional 5 mg/kg doses administered at 2 and 6 weeks after the initial infusion, for treatment of fistula(s) in Crohn's disease. If a patient does not respond after these 3 doses, additional treatment with **REMSIMA** should not be given. There are insufficient safety and efficacy data for the use of **REMSIMA** beyond the recommended duration (see section 4.1).

Strategies for continued treatment are:
- additional infusions of 5 mg/kg every 8 weeks, or
- re-administration if signs and symptoms of the disease recur, followed by intravenous infusions of 5 mg/kg every 8 weeks (see **Re-administration** below and section 4.4).

In Crohn's disease, experience with re-administration if signs and symptoms of the disease recur is limited. Comparative data on the benefit/risk of alternative strategies for combined treatment are lacking. Continued therapy should be considered carefully in patients who show no evidence of therapeutic benefit after dose adjustment.

Adult or paediatric ulcerative colitis
Initially a 5 mg/kg intravenous infusion (see **Method of administration** below), followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the initial infusion, then every 8 weeks thereafter. Data available suggest that continued therapy with **REMSIMA** should be reassessed carefully if no response has occurred after 14 weeks.

Re-administration for Crohn's disease and rheumatoid arthritis
If signs and symptoms of the disease recur, **REMSIMA** can be re-administered within 16 weeks after the last infusion. In patients with Crohn's disease, re-administration of **REMSIMA** with a medicine-free interval of 2 to 4 years following a previous infusion has been associated with a delayed hypersensitivity reaction (see section 4.8, **Delayed hypersensitivity**). After a medicine-free interval of 16 weeks to 2 years, the risk of delayed hypersensitivity following re-administration is unknown. Therefore, re-administration cannot be recommended after a medicine-free interval of 16 weeks.

Re-administration for ankylosing spondylitis
Data to support re-administration, other than every 6 to 8 weeks, are not available.

Re-administration for psoriatic arthritis, psoriasis and ulcerative colitis
Data to support re-administration, other than every 8 weeks, are not available.

Method of administration
For adult and paediatric patients, administer the intravenous infusion solution over a period of not less than 2 hours. All patients administered **REMSIMA** must be observed for at least 1 to 2 hours after infusion for side effects. Medication, an artificial airway and other appropriate materials must be available for the treatment of these side effects (see section 4.4, **Infusion reactions and hypersensitivity**).

Shortened infusions across adult indications
In carefully selected adult patients who have tolerated at least 3 initial 2-hour intravenous infusions of **REMSIMA** (induction phase) and are receiving maintenance therapy, consideration may be given to administer subsequent infusions over a period of not less than 1 hour. Shortened infusions at doses > 6 mg/kg have not been studied.

For preparation and administration instructions, see section 6.6.

4.3 Contraindications
REMSIMA is contraindicated in:
- Patients with a history of hypersensitivity to infliximab, to other murine proteins, or to any of the excipients listed in section 6.1.
- Patients with tuberculosis (TB) or other severe infections such as abscesses, sepsis, or opportunistic infections. Patients must be closely monitored for infections, including tuberculosis before, during and after treatment with **REMSIMA**, in accordance with local recommendations. Treatment with **REMSIMA** must be discontinued if a patient develops serious infections or sepsis.
- Patients with moderate or severe heart failure (NYHA class III/IV) (see section 4.4).
- Concomitant use of anakinra (see section 4.4).
- Concomitant use of live vaccines (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

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

Infusion reactions and hypersensitivity

REMSIMA has been associated commonly with acute infusion-related reactions, including anaphylactic shock, and uncommonly with delayed hypersensitivity reactions (see section 4.8). Therefore, all patients receiving **REMSIMA** should be closely observed for side effects. Urticaria, dyspnoea and hypotension have occurred in association with **REMSIMA** infusion.

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 epinephrine (adrenaline), antihistamines, corticosteroids and an artificial airway must be available. Patients may be pre-treated with e.g. an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects (see section 4.2, **Method of administration**).

Antibodies to **REMSIMA** may develop and have been associated with an increased frequency of infusion reactions. A low proportion of the infusion reactions was serious allergic reactions. An association between development of antibodies to **REMSIMA** and reduced duration of response has also been observed. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to **REMSIMA** 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 **REMSIMA** treatment are at greater risk of developing these antibodies. Antibodies to **REMSIMA** 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).

Patients who develop antibodies to **REMSIMA** are more likely to develop infection-related reactions.

In clinical studies, delayed hypersensitivity reactions have been reported after treatment interruption for less than one year. This has been reported in as much as 25 % of Crohn's disease patients who were treated following a year period of withdrawal treatment. Available data suggest an increased risk for delayed hypersensitivity with increasing **REMSIMA**-free interval.
Signs and symptoms include myalgia and/or rash within 12 days following re-treatment. Some people also experienced pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and/or headache. These effects have sometimes been described as serum sickness-like reactions.
Patients should be advised to seek immediate medical advice if they experience any delayed adverse event (see section 4.8). If patients are re-treated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.

Infections

Bacterial (including sepsis and pneumonia), mycobacterial (tuberculosis), invasive fungal and opportunistic infections (such as listeriosis and legionella), including fatalities have been reported in patients receiving TNF blocking medicines, including **REMSIMA**. Some of these serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to the underlying disease, could predispose them to infections. For patients who have resided or travelled to regions where invasive fungal infections such as histoplasmosis,

coccidiomycosis or blastomycosis are endemic, the benefits and risks of **REMSIMA** treatment should be carefully considered before initiation of **REMSIMA** therapy.

REMSIMA should not be given to patients with clinically important, active infections. Caution should be exercised when considering the use of **REMSIMA** in patients with chronic infection or history of recurrent infection. Patients should be advised of and avoid exposure to potential risk factors for infection as appropriate.

Tuberculosis
Patients should be evaluated for tuberculosis risk factors (including close contact with a person with active tuberculosis) and tested for latent tuberculosis infection prior to treatment with **REMSIMA**. Treatment of latent tuberculosis infection should be initiated prior to therapy with **REMSIMA** (see section 4.3).

Anti-tuberculosis therapy should be considered prior to initiation of **REMSIMA** in patient with a past history of latent or active tuberculosis in whom an alternate course of treatment cannot be confirmed.

Tests for latent tuberculosis may yield false negative results, especially in patients who are immune-compromised or severely ill. Prior to initiating **REMSIMA**, treatment for latent TB should be considered in patient with significant risk factors for TB despite a negative test for latent TB. The decision to initiate anti-TB therapy in these patients should only be made following consultation with the medical practitioner with expertise in the treatment of TB and taking into account both the risk for latent TB infection and the risks of anti-TB therapy. Patients receiving **REMSIMA** should be monitored closely for signs and symptoms of active TB during and after treatment, including patients who tested negative for latent TB infection.

Human antichimeric antibody (HACA) development
In a study of Crohn's disease patients treated with infliximab and evaluated for HACA; a significant proportion was HACA-positive (the majority at low titre, ≤ 1:20). Patients were more likely to experience an infusion reaction if HACA-positive. The incidence of positive HACA responses was lower amongst Crohn's disease patients who received immunosuppressant therapies such as corticosteroids than amongst those who did not receive these medicines.

Invasive fungal infections
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 systemic illness, and a medical practitioner with expertise in the diagnosis and treatment of invasive fungal infections should be consulted at an early stage when investigating these patients.

Invasive fungal infections may present as disseminated rather than localised disease, and antigen and antibody testing may be negative in some patients with active infection. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed taking into account both the risk for severe fungal infection and the risks of antifungal therapy.

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

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

Hepatobiliary events
Cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of **REMSIMA**. Isolated cases of liver failure resulting in liver transplantation or death have occurred. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or ALT elevations ≥ 5 times the upper limit of normal develop(s), **REMSIMA** should be discontinued, and a thorough investigation of the abnormality should be undertaken.

Concurrent administration of REMSIMA and anakinra
Neutropenia and serious infections have been observed in clinical studies with concurrent use of anakinra and etanercept, another TNFα-blocking medicine, with no added clinical benefit when compared to etanercept alone. Due to the nature of the adverse events seen with combination of etanercept and anakinra therapy, similar toxicities from the combination of anakinra and other TNFα-blocking medicines may also result.
The combination of **REMSIMA** and anakinra is therefore not recommended (see section 4.3).

Concurrent administration of REMSIMA and abatacept
In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of **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 **REMSIMA**. The concomitant use of **REMSIMA** with these biologicals is not recommended because of the possibility of an increased risk of infection, and other potential pharmacological interactions.

Switching between biological Disease-Modifying Antirheumatic Drugs (DMARDs)
Care should be taken and patients should continue to be monitored when switching from one biological to another, since overlapping biological activity may further increase the risk for adverse events, including infection.

Live vaccines/therapeutic infectious medicines
In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines can result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with **REMSIMA** is not recommended (see section 4.3).

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. At least a six month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab (see section 4.6).

Other uses of therapeutic infectious medicines 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 medicines not be given concurrently with **REMSIMA**.

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 section 4.8). Patients who develop anti-double-stranded DNA (anti-dsDNA) and/or symptoms suggestive of a lupus-like syndrome have had resolution of symptoms and disappearance of the anti-dsDNA after discontinuation of **REMSIMA** therapy.

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

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

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

With the current knowledge, a risk for the development of lymphomas or other malignancies in patients treated with a TNF-blocking medicine cannot be excluded (see section 4.8). Caution should be exercised when considering **REMSIMA** therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

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

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking medicines (initiation of therapy ≤18 years of age), including **REMSIMA** in the post-marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of

malignancies in patients treated with **REMSIMA** cannot be excluded.

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

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including **REMSIMA** (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

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

All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. With current data, it is not known if **REMSIMA** 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.

Heart failure
In patients with mild heart failure (NYHA class I/II) **REMSIMA** should be used with caution. Patients should be closely monitored and **REMSIMA** must be discontinued in patients who develop new or worsening symptoms of heart failure (see sections 4.3 and 4.8).

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

Other
There is limited safety experience of infliximab treatment in patients who have undergone surgical procedures, including arthroplasty. The long half-life of infliximab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on **REMSIMA** should be closely monitored for infections, and appropriate actions should be taken.

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

Special populations
Older people (≥ 65 years)
The incidence of serious infections in infliximab-treated patients 65 years and older was greater than in those under 65 years of age. Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly (see section 4.8).

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

Vaccinations
It is recommended that paediatric patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating **REMSIMA** therapy.

REMSIMA has not been studied in children with Crohn's disease less than 6 years of age or in children with juvenile rheumatic arthritis.

Sodium content
REMSIMA contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

Sucrose
REMSIMA contains sucrose which may influence the glycaemic control of patients with diabetes mellitus.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take **REMSIMA**.

4.5 Interaction with other medicines and other forms of interaction
No interaction studies have been performed.

In rheumatoid arthritis, psoriatic arthritis and Crohn's disease patients, there are indications that concomitant use of methotrexate 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 medicines used to treat the same conditions as **REMSIMA**, including anakinra and abatacept, is not recommended (see sections 4.3 and 4.4).

It is recommended that live vaccines not be given concurrently with **REMSIMA**. It is also recommended that live vaccines not be given to infants after *in utero* exposure to infliximab for at least 6 months following birth (see sections 4.3 and 4.4).

It is recommended that therapeutic infectious medicines not be given concurrently with **REMSIMA** (see section 4.4).

4.6 Fertility, pregnancy and lactation
Safety during pregnancy and lactation has not been established.

Women of childbearing potential
Women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last **REMSIMA** treatment.

Pregnancy
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 at least 12 months after birth (see sections 4.4 and 4.5). If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant. Cases of agranulocytosis have also been reported (see section 4.8).

Breastfeeding
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 breastfeeding.

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
REMSIMA may have an influence on the ability to drive and use machines. Dizziness may occur following administration of **REMSIMA**.

4.8 Undesirable effects
a) Summary of the safety profile
Upper respiratory tract infection was the most common adverse drug reaction (ADR) reported in clinical trials, occurring in 25,3 % of infliximab-treated patients compared with 16,5 % of control patients. The most serious ADRs associated with the use of TNF blockers that have been reported for infliximab include hepatitis B virus (HBV) reactivation, congestive heart failure (CHF), serious infections (including sepsis, opportunistic infections and TB), serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, HSTCL, leukaemia, Merkel cell carcinoma, melanoma, paediatric malignancy, sarcoidosis/sarcoid-like reaction, intestinal or perianal abscess (in Crohn's disease), and serious infusion reactions (see section 4.4).

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

data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse reactions in clinical studies and from post-marketing experience

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

Metabolism and nutrition disorders	
Uncommon:	Dyslipidaemia.
Psychiatric disorders	
Common:	Depression, insomnia.
Uncommon:	Amnesia, agitation, confusion, somnolence, nervousness.
Rare:	Apathy.
Nervous system disorders	
Very common:	Headache.
Common:	Vertigo, dizziness, hypaesthesia, paraesthesia.
Uncommon:	Seizure, neuropathy.
Rare:	Transverse myelitis, central nervous system demyelinating disorders (multiple sclerosis-like disease and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy).
Eye disorders	
Common:	Conjunctivitis.
Uncommon:	Keratitis, periorbital oedema, hordeolum.
Rare:	Endophthalmitis.
Not known:	Transient visual loss occurring during or within 2 hours of infusion.
Cardiac disorders	
Common:	Tachycardia, palpitation.
Uncommon:	Cardiac failure (new onset or worsening), arrhythmia, syncope, bradycardia.
Rare:	Cyanosis, pericardial effusion.
Not known:	Myocardial ischaemia/myocardial infarction.
Vascular disorders	
Common:	Hypotension, hypertension, ecchymosis, hot flush, flushing.

Uncommon:	Peripheral ischaemia, thrombophlebitis, haematoma.
Rare:	Circulatory failure, petechia, vasospasm.
Respiratory, thoracic and mediastinal disorders	
Very common:	Upper respiratory tract infection, sinusitis.
Common:	Lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, epistaxis.
Uncommon:	Pulmonary oedema, bronchospasm, pleurisy, pleural effusion.
Rare:	Interstitial lung disease (including rapidly progressive disease, lung fibrosis and pneumonitis).
Gastrointestinal disorders	
Very common:	Abdominal pain, nausea.
Common:	Gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastro-oesophageal reflux, constipation.
Uncommon:	Intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis.
Hepatobiliary disorders	
Common:	Hepatic function abnormal, transaminases increased.
Uncommon:	Hepatitis, hepatocellular damage, cholecystitis.
Rare:	Autoimmune hepatitis, jaundice.
Not known:	Liver failure.
Skin and subcutaneous tissue disorders	
Common:	New onset or worsening psoriasis including pustular psoriasis (primarily palm and soles), urticaria, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia.
Uncommon:	Bullous eruption, onychomycosis, seborrhoea, rosacea, skin papilloma, hyperkeratosis, abnormal skin pigmentation.
Rare:	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, furunculosis, linear IgA bullous dermatosis (LABD), acute generalised exanthematous pustulosis (AGEP), lichenoid reactions.
Not known:	Worsening of symptoms of dermatomyositis.

Musculoskeletal and connective tissue disorders	
Common:	Arthralgia, myalgia, back pain.
Renal and urinary disorders	
Common:	Urinary tract infection.
Uncommon:	Pyelonephritis.
Reproductive system and breast disorders	
Uncommon:	Vaginitis.
General disorders and administration site conditions	
Very common:	Infusion-related reaction, pain.
Common:	Chest pain, fatigue, fever, injection site reaction, chills, oedema.
Uncommon:	Impaired healing.
Rare:	Granulomatous lesion.
Investigations	
Uncommon:	Autoantibody positive.
Rare:	Complement factor abnormal.

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

c) Description of selected adverse reactions

Infusion-related reactions

An infusion-related reaction was defined as any adverse event occurring during an infusion or within 1 hour after an infusion. In clinical studies, 18 % of infliximab-treated patients compared with 5 % of placebo-treated patients experienced an infusion-related reaction.

Overall, a higher proportion of patients receiving infliximab monotherapy experienced an infusion-related reaction compared to patients receiving infliximab with concomitant immunomodulators.

Approximately 3 % of patients discontinued treatment due to infusion-related reactions and all patients recovered with or without medical therapy. Of infliximab-treated patients who had an infusion reaction during the induction period, through week 6, 27 % experienced an infusion reaction during the maintenance period, week 7 through week 54. Of patients who did not have an infusion reaction during the induction period, 9 % experienced an infusion

reaction during the maintenance period.

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

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

Delayed hypersensitivity
In clinical studies delayed hypersensitivity reactions have been uncommon and have occurred after infliximab-free intervals of less than 1 year. In the psoriasis studies, delayed hypersensitivity reactions occurred early in the treatment course. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients experiencing pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and headache.

Immunogenicity
Patients who developed antibodies to infliximab were more likely (approximately 2- to 3- fold) to develop infusion-related reactions. Use of concomitant immunosuppressant medicines appeared to reduce the frequency of infusion-related reactions.

In clinical studies using single and multiple infliximab doses ranging from 1 to 20 mg/kg, antibodies to infliximab were detected in 14 % of patients with any immunosuppressant therapy, and in 24 % of patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, 8 % of patients developed antibodies to infliximab. In psoriatic arthritis patients who received 5 mg/kg with and without methotrexate, antibodies occurred overall in 15 % of patients (antibodies occurred in 4 % of patients receiving methotrexate and in 26 % of patients not receiving methotrexate at baseline). In Crohn's disease patients who received maintenance treatment, antibodies to infliximab occurred overall in 3,3 % of patients receiving immunosuppressants and in 13,3 % of patients not receiving immunosuppressants. The antibody incidence was 2- to 3- fold higher for patients treated episodically. Due to methodological limitations, a negative assay did not exclude the presence of antibodies to infliximab. Some patients who developed high titres of antibodies to infliximab had evidence of reduced efficacy. In psoriasis patients treated with infliximab as a maintenance regimen in the absence of concomitant immunomodulators, approximately 28 % developed antibodies to infliximab (see section 4.4**, Infusion reactions and hypersensitivity**).

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

In clinical studies 36 % of infliximab-treated patients were treated for infections compared with 25 % of placebo-treated patients.

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

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

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

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

Heart failure
There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. There have also been post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.

Hepatobiliary events
Mild or moderate elevations of ALT and AST have been observed in patients receiving infliximab without progression to severe hepatic injury. Elevations of ALT ≥ 5 x upper limit of normal (ULN) have been observed. Elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving infliximab than in controls, both when infliximab was given as monotherapy and when it was used in combination with other immunosuppressive medicines. Most aminotransferase abnormalities were transient; however, a small number of patients experienced more prolonged elevations. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of infliximab, or modification of concomitant therapy. In post-marketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving infliximab (see section 4.4).

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

d) Paediatric population

Juvenile rheumatoid arthritis patients

Infusion reactions

Infusion reactions occurred in 35 % of patients with juvenile rheumatoid arthritis receiving 3 mg/kg compared with 17,5 % of patients receiving 6 mg/kg. In the 3 mg/kg infliximab group, 4 out of 60 patients had a serious infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among the serious infusion reactions). In the 6 mg/kg group, 2 out of 57 patients had a serious infusion reaction, one of whom had a possible anaphylactic reaction (see section 4.4).

Immunogenicity

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

Infections

Infections occurred in 68 % (41/60) of children receiving 3 mg/kg over 52 weeks, 65 % (37/57) of children receiving infliximab 6 mg/kg over 38 weeks and 47 % (28/60) of children receiving placebo over 14 weeks (see section 4.4).

Paediatric Crohn's disease patients

The following adverse events were reported more commonly in paediatric Crohn's disease patients than in adult Crohn's disease patients: anaemia, blood in stool, leucopenia, flushing, viral infection, neutropenia, bone fracture, bacterial infection, and respiratory tract allergic reaction. Other special considerations are discussed below.

Infusion-related reactions

17,5 % of randomised patients experienced 1 or more infusion reactions. There were no serious infusion reactions, and 2 subjects had non-serious anaphylactic reactions.

Immunogenicity

Antibodies to infliximab were detected in 3 (2,9 %) paediatric patients.

Infections

Infections were reported in 56,3 % of randomised subjects–treated with infliximab. Infections were reported more frequently for subjects who received q8 week as opposed to q12 week infusions (73,6 % and 38,0 %, respectively), while serious infections were reported for 3 subjects in the q8 week and 4 subjects in the q12 week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Three cases of pneumonia (1 serious) and 2 cases of herpes zoster (both non-serious) were reported.

Paediatric ulcerative colitis patients

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

Infusion-related reactions
Overall, 8 (13,3 %) of 60 treated patients experienced one or more infusion reactions, with 4 of 22 (18,2 %) in the q8 week and 3 of 23 (13,0 %) in the q12 week treatment maintenance group. No serious infusion reactions were reported. All infusion reactions were mild or moderate in intensity.
Immunogenicity
Antibodies to infliximab were detected in 4 (7,7 %) patients through week 54.
Infections
Infections were reported in 31 (51,7 %) of 60 treated patients and 22 (36,7 %) required oral or parenteral antimicrobial treatment. The proportion of patients with infections was similar to that in the paediatric Crohn's disease study but higher than the proportion in the adults ulcerative colitis studies. The overall incidence of infections was 13/22 (59 %) in the every 8-week maintenance treatment group and 14/23 (60,9 %) in the every 12 week maintenance treatment group. Upper respiratory tract infection (7/60 [12 %]) and pharyngitis (5/60 [8 %]) were the most frequently reported respiratory system infections. Serious infections were reported in 12 % (7/60) of all treated patients.
There were more patients in the 12 to 17 years age group than in the 6 to 11 years age group (45/60 [75,0 %]) vs.15/60 [25,0 %]). While the numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on safety events, there were higher proportions of patients with serious adverse events and discontinuation due to adverse events in the younger age group than in the older age group. While the proportion of patients with infections was also higher in the younger age group, for serious infections, the proportions were similar in the two age groups.
Overall proportions of adverse events and infusion reactions were similar between the 6 to 11 and 12 to 17 years age groups.

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

e) Additional information on special populations
In rheumatoid arthritis clinical studies, the incidence of serious infections was greater in infliximab plus methotrexate-treated patients 65 years and older (11,3 %) than in those under 65 years of age (4,6 %). In patients treated with methotrexate alone, the incidence of serious infections was 5,2 % in patients 65 years and older compared to 2,7 % in patients under 65 (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
For reporting of side effects directly to the HCR, contact +27 11 635 0134 or email Adcock.aereports@adcock.com.

4.9 Overdose
No case of overdose has been reported.
Single doses up to 20 mg/kg have been administered without direct toxic effects.
In case of overdosage it is recommended that patients be monitored for any signs or symptoms of adverse reactions or effects, and appropriate symptomatic and supportive treatment be started immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.30.1 Biologicals - Antibodies
Pharmacotherapeutic group: immunosuppressants, tumour necrosis factor alpha (TNFα) inhibitors, ATC code: L04AB02
REMSIMA is a biosimilar medicine.

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 ($TNF_ß$).

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.

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

5.2 Pharmacokinetic properties

Dose proportional increases in the maximum serum concentration (C_{max}) and area under the concentration-time curve (AUC) with single intravenous infusions of 1, 3, 5, 10 or 20 mg/ kg of infliximab were yielded. The volume of distribution at steady state (median V_d of 3,0 to 4,1 litres) did not depend on the administered dose and indicated that infliximab is predominantly distributed within the vascular compartment. No time-dependency of the pharmacokinetics was observed. Elimination pathways have not been characterised for infliximab. Unchanged infliximab was not detected in urine. No major age- or weight-related differences in clearance or volume of distribution were observed in rheumatoid arthritis patients.
The pharmacokinetics of infliximab in elderly patients have not been studied. Studies have not been performed in patients with liver or renal disease.

The median C_{max} values were 77, 118 and 277 µg/ml at single doses of 3, 5, or 10 mg/kg. The median terminal half-life at these doses ranged from 8 to 9,5 days. Infliximab could be detected in the serum for at least 8 weeks after a single infusion in most patients.

When the 3-dose regimen was followed, a slight accumulation of infliximab was observed in the serum after the second dose and thereafter, no further clinically relevant accumulation was

observed. Infliximab could be detected in the serum for 12 weeks (range 4 – 28 weeks) after administration of the regimen in most fistulising Crohn's disease patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium dihydrogen phosphate monohydrate
di-Sodium hydrogen phosphate dihydrate
Polysorbate 80

6.2 Incompatibilities

In the absence of compatibility studies, **REMSIMA** must not be mixed with other medicines.

6.3 Shelf life

Before reconstitution

5 years at 2 °C– 8 °C.

REMSIMA may be stored at temperatures up to a maximum of 25 °C for a single period of up to 6 months, but not exceeding the original expiry date. The new expiry date must be written on the carton. Upon removal from refrigerated storage, **REMSIMA** must not be returned to refrigerated storage.

After reconstitution

Chemical and physical in use stability of the reconstituted solution has been demonstrated for 24 hours at 25 °C. From a microbiological point of view, the product should be used as soon as possible but within 3 hours of reconstitution and dilution. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 °C to 8 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).
For storage conditions up to 25 °C before reconstitution of the medicinal product, see section 6.3.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 ml type I clear glass vial with a grey butyl rubber stopper and an aluminium flip-off seal with a white polypropylene flip-off cap, packed in an outer carton.

6.6 Special precautions for disposal and other handling

Preparation and administration - USE ASEPTIC TECHNIQUE

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

REMSIMA does not contain preservatives. After reconstitution the vials should therefore be used immediately and not re-entered or stored. The diluent that should be used for reconstitution is 10 ml of sterile water for injection. The total dose of the reconstituted product must be further diluted with 0,9 % sodium chloride injection to 250 ml. The infusion concentration should range between 0,4 and 4 mg/ml. Infusion of **REMSIMA** should begin within 3 hours of preparation.

1. Calculate the required dose and the number of **REMSIMA** vials that will be needed. Each vial contains 100 mg of infliximab. Calculate the total volume of reconstituted **REMSIMA** solution required.
2. Under aseptic conditions, reconstitute each **REMSIMA** vial with 10 ml of sterile water for injection. Use a syringe equipped with a 21-gauge (0,8 mm) or smaller needle. Upon reconstitution, each ml of reconstituted solution contains 10 mg of infliximab. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the needle of the syringe into the vial through the centre of the rubber stopper. Direct the stream of sterile water for injection to the glass wall of the vial. Swirl the solution gently by rotating the vial to dissolve the lyophilised powder. Avoid vigorous or prolonged agitation.
   DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. Check that the reconstituted solution is colourless to light yellow and opalescent. As infliximab is a protein, the solution may develop a few fine translucent particles. Do not use if discolouration, opaque particles or other foreign particles are present.
3. Dilute the total volume of the reconstituted **REMSIMA** solution to 250 ml with 0,9 % *m/v* sodium chloride solution for infusion, by withdrawing a volume of 0,9 % *m/v* sodium chloride injection, equal to the volume of reconstituted **REMSIMA** solution from the 0,9 % *m/v* sodium chloride injection 250 ml glass bottle or bag. Slowly add the total volume of the **REMSIMA** reconstituted solution to the 250 ml infusion bottle or bag. Mix gently. For volumes greater than 250 ml, either use a larger infusion bag (e.g. 500 ml, 1000 ml) or use multiple 250 ml infusion bags to ensure that the concentration of the infusion solution does not exceed 4 mg/ml. If stored refrigerated after reconstitution and dilution, the infusion solution must be allowed to equilibrate at room temperature to 25 °C for 3 hours prior to Step 4 (infusion). Storage beyond 24 hours at 2 °C - 8 °C applies to preparation of **REMSIMA** in the infusion bag only.
4. The infusion solution has to be administered over a period of not less than the infusion time recommended (see section 4.2, **Method of administration**). Only an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1,2 µm or less) should be used. Since there are no preservatives present, it is recommended that the administration of the solution for infusion be started as soon as possible and within 3 hours of reconstitution and dilution. Any unused portion of the infusion solution should not be stored for re-use. If reconstitution and dilution of **REMSIMA** are performed under strict aseptic conditions, **REMSIMA** infusion solution can be used within 24 hours if stored at 2 to 8 °C.
5. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of **REMSIMA** with other medicines. **REMSIMA** should not be infused concomitantly with other medicines in the same intravenous line.
6. **REMSIMA** should be inspected visually for discolouration and particulate matter prior to administration, whenever solution and container permit. The solution should not be used if visibly opaque particles, discolouration or other foreign particulates are observed.
7. Discard any unused portion of the infusion solution.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
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Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER
52/30.1/0309

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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10. DATE OF REVISION OF THE TEXT
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