PROFESSIONAL INFORMATION FOR

REMIFLIX

SCHEDULING STATUS

S4

BOXED WARNING

SERIOUS INFECTIONS

Patients treated with REMIFLIX are at increased risk for developing serious infections that may lead to hospitalisation or death (see **section 4.4** and **section 4.8**). Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

REMIFLIX should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before REMIFLIX use and during therapy. Treatment for latent infection should be initiated prior to REMIFLIX use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localised, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacteria, viral and other infections due to opportunistic pathogens, including *Legionella* and *Listeria*.

The risks and benefits of treatment with REMIFLIX should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with REMIFLIX, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with Tumour necrosis factor (TNF) blockers, including REMIFLIX (see **section 4.4**). Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF-blockers including REMIFLIX. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported REMIFLIX cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males.

1. NAME OF THE MEDICINE

REMIFLIX 100 mg, Lyophilised powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITIVE COMPOSITION

Each single-dose vial contains infliximab* 100 mg.

One vial contains 100 mg of infliximab*. After reconstitution, each mL contains 10 mg of infliximab.

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

No preservatives.

Contains sugar (sucrose 500 mg per vial).

For full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Lyophilised powder for concentrate for solution for infusion.

Before reconstitution: REMIFLIX is supplied as a sterile, white to pale yellow, lyophilised powder for intravenous infusion.

After reconstitution: The solution is colourless to straw coloured, clear to opalescent solution, essentially free of visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

In combination with methotrexate, REMIFLIX is indicated for:

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

In patients with active rheumatoid arthritis despite treatment with methotrexate.

- Use in early rheumatoid arthritis in patients with severe, active, and progressive disease not previously treated with methotrexate or other Disease-Modifying Anti-rheumatic Drugs (DMARDs).

Ankylosing spondylitis

REMIFLIX is indicated for:

- Reducing signs and symptoms in patients with active ankylosing spondylitis
- Improvement in physical function in patients with active disease.

Psoriatic arthritis

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

- reduction of signs and symptoms of psoriatic arthritis
- induction of major clinical response in active psoriatic arthritis
- inhibition of the 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.

REMIFLIX 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, REMIFLIX 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, REMIFLIX is indicated for:

- reduction of signs and symptoms
- induction and the maintenance clinical remission
- Induction of mucosal healing
- Improvement in quality of life.

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

Fistulising Crohn's disease

In patients with fistulising Crohn's disease, **REMIFLIX** in indicated for:

- reduction in the number of draining enterocutaneous and rectovaginal fistulas and maintaining 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, REMIFLIX is indicated for:

- reduction of signs and symptoms,
- induction and maintenance of clinical remission
- induction of mucosal healing
- reduction or elimination of administration of corticosteroid
- Improvement in quality of life
- 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.

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

REMIFLIX should be administered intravenously. Patients treated with REMIFLIX should be given the patient information leaflet.

During REMIFLIX 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. REMIFLIX 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 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 REMIFLIX 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.

Adult and 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 REMIFLIX should be reassessed carefully if no response has occurred after 14 weeks.

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 to 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 REMIFLIX 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. REMIFLIX 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 REMIFLIX should not be given. There are insufficient safety and efficacy data for the use of REMIFLIX 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.

Special populations

Elderly population

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

Renal and/or hepatic impairment

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

Paediatric population

Crohn's disease (6 to 17 years)

A paediatric Crohn's disease pharmacokinetic study was conducted in patients aged 11 to 17 years old. No notable differences in single-dose pharmacokinetics were observed between paediatric and adult Crohn's disease patients.

The safety and efficacy of infliximab have not been studied in children with Crohn's disease below the age of 6 years.

Ulcerative colitis (6 to 17 years)

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

Re-administration for Crohn's disease and rheumatoid arthritis

If the signs and symptoms of the disease recur, REMIFLIX can be re-administered within 16 weeks following the last infusion. In patients with Crohn's disease, re-administration of REMIFLIX 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 psoriatic arthritis and ulcerative colitis

The safety and efficacy of re-administration, other than every 8 weeks, has not been established.

Re-administration for ankylosing spondylitis

The safety and efficacy of re-administration, other than every 6 to 8 weeks, has not been established.

Re-administration for psoriasis

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

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

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 REMIFLIX 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 REMIFLIX (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

REMIFLIX is contraindicated in:

- Patients with known hypersensitivity to infliximab or to any of the excipients in REMIFLIX (see **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 REMIFLIX, in accordance with local recommendations. Treatment with REMIFLIX must be discontinued if a patient develops serious infections or sepsis
- Patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), infliximab treatment at 10 mg/kg was associated with an

increased incidence of death and hospitalisation due to worsening heart failure (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.

Serious infections

Patients treated with REMIFLIX are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalisation or death.
Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections have been observed in patients treated with infliximab, as in REMIFLIX. Some of these infections have been fatal; the most frequently reported opportunistic infections with a mortality rate of > 5 % include pneumocystosis, candidiasis, listeriosis and aspergillosis.

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

Opportunistic infections (such as listeriosis and legionella), bacterial (including sepsis and pneumonia), mycobacterial (tuberculosis), invasive fungal, viral, or parasitic organisms

including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF-blockers, including REMIFLIX. Patients have frequently presented with disseminated rather than localised disease.

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

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

Treatment with REMIFLIX should not be initiated in patients with an active infection, including clinically important localised infections. Patients who develop a new infection while undergoing treatment with infliximab, should be monitored closely and undergo a complete diagnostic evaluation. Administration of infliximab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. The risks and benefits of the treatment should be considered prior to initiating therapy in patients:

- with chronic or recurrent infection,
- who have been exposed to tuberculosis,
- with a history of an opportunistic infection,
- who have resided or travelled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, occidioidomycosis, or blastomycosis, or with underlying conditions that may predispose them to infection.

The risks and benefits of treatment with REMIFLIX should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Tuberculosis (TB)

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving infliximab, including patients who have previously received treatment for latent or active tuberculosis. It should be noted that in the majority of these reports tuberculosis was extrapulmonary, presenting as either local or disseminated disease. 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 REMIFLIX. Treatment of latent tuberculosis infection should be initiated prior to therapy with REMIFLIX (see **section 4.3**). Furthermore, a history of previous tuberculosis, HIV infection, or a diagnosis of latent tuberculosis infection pose a risk for reactivation of tuberculosis diseases and appropriate preventative therapy is indicated, regardless of HIV status.

Treatment of latent tuberculosis infection prior to therapy with TNF-blocking medicines has been shown to reduce the risk of TB reactivation during therapy.

Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating REMIFLIX, even for patients previously vaccinated with Bacille Calmette-Guérin (BCG).

Anti-tuberculosis therapy should also be considered prior to initiation of REMIFLIX in patients with a history of latent or active TB in whom an adequate 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 REMIFLIX, 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 REMIFLIX should be monitored closely for signs and symptoms of active TB during and after treatment, including patients who tested negative for latent TB infection.

Some cases of active tuberculosis have been reported in patients treated with infliximab during and after treatment for latent tuberculosis.

All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g. persistent cough, wasting/weight loss, low-grade fever) appear during or after infliximab treatment.

Tuberculosis should be strongly considered in patients who develop a new infection during REMIFLIX treatment, especially in patients who have previously or recently travelled to countries with a high prevalence of TB or who have had close contact with a person with active TB.

Invasive fungal infections

In patients treated with REMIFLIX 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.

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. 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.

Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a medical practitioner with expertise in the diagnosis and treatment of invasive fungal infections and should consider both the risk for severe fungal infection and the risks of antifungal therapy.

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

Fistulising Crohn's disease

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

Malignancies and lymphoproliferative disorders

In the controlled portions of clinical trials of all the TNF-blocking medicines, more cases of lymphoma have been observed among patients receiving a TNF-blocker compared with control patients. During clinical studies of REMIFLIX across all approved indications the incidence of lymphoma in REMIFLIX-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 longstanding, highly active, inflammatory disease, which complicates risk estimation. In the controlled portions of clinical trials of some TNF-blocking medicines including REMIFLIX, more malignancies (excluding lymphoma and non-melanoma skin cancer [NMSC]) have been observed in patients receiving those TNF-blockers compared with control patients.

The most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among infliximab treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.

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 REMIFLIX 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 infliximab in the post-marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in patients treated with TNF-blockers cannot be excluded.

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

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

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

All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. Current data do not indicate that infliximab treatment influences the risk for developing dysplasia or colon cancer.

Since the possibility of increased risk of cancer development in patients with newly diagnosed dysplasia treated with infliximab, as in REMFLIX, is not established, the risk and benefits of continued therapy to the individual patients should be carefully considered by the clinician.

Hepatitis B Virus (HBV) reactivation

Use of TNF-blockers, including REMIFLIX, has been associated with reactivation of HBV in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. Most of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which

may also contribute to HBV reactivation.

Patients should be tested for HBV infection before initiating TNF-blocker therapy, including REMIFLIX. For patients who test positive for hepatitis B surface antigen, consultation with a doctor with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF-blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF-blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF-blocker therapy after HBV reactivation is controlled, is not known. Therefore, prescribers should exercise caution when considering resumption of TNF-blocker therapy in this situation and monitor patients closely.

Hepatobiliary events

Cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of REMIFLIX.

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), REMIFLIX should be discontinued, and a thorough investigation of the abnormality should be undertaken.

Heart failure

It has been reported that REMIFLIX has been associated with adverse outcomes in patients with heart failure and should be used in patients with heart failure only after consideration of

other treatment options. The results of a randomised study evaluating the use of infliximab in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg infliximab, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMIFLIX. 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. If a decision is made to administer REMIFLIX to patients with heart failure, they should be closely monitored during therapy, and REMIFLIX should be discontinued if new or worsening symptoms of heart failure appear (see **section 4.3** and **4.8**).

Infusion reactions and Hypersensitivity

It has been reported that REMIFLIX has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalisation in some cases. Most hypersensitivity reactions, which include, urticaria, dyspnoea, and/or hypotension, have occurred during or within 2 hours of REMIFLIX 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 adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.

Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions. A low proportion of the infusion reactions was serious allergic reactions.

An association between development of antibodies to infliximab and reduced duration of response has also been observed. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and a reduction in the frequency of infusion reactions. The effect of concomitant immunomodulator therapy was more profound in episodically-treated patients than in patients given maintenance therapy. Patients who discontinue immunosuppressants prior to or during infliximab treatment are at greater risk of developing these antibodies. Antibodies to infliximab cannot always be detected in serum samples. If serious reactions occur, symptomatic treatment must be given and further infliximab infusions must not be administered (see **section 4.8**)

It has been reported that in rheumatoid arthritis, clinical trials, re-administration of REMIFLIX after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment. In general, the benefit-risk of re-administration of REMIFLIX after a period of no treatment, especially as a re-induction regimen at weeks 0, 2 and 6, should be carefully considered.

Cases of 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 infliximab-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 reaction (see **section 4.8**). If patients are re-treated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.

Haematologic reactions

Cases of leucopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMIFLIX.

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, bruising, bleeding, pallor) while on REMIFLIX.

Discontinuation of infliximab therapy should be considered in patients who develop significant haematologic abnormalities.

Neurologic reactions

Use of TNF-blocking medicines, including REMIFLIX, has been associated with new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disorders, including multiple sclerosis and optic neuritis, 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 REMIFLIX therapy.

Concurrent administration with anakinra

Serious infections and neutropenia were reported in clinical studies with concurrent use of anakinra and another TNFα-blocking medicine, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse reactions seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNFα-blocking medicines. Therefore, the combination of REMIFLIX and anakinra is not recommended (see **section 4.3**).

Concurrent administration with abatacept

Concurrent administration of TNF-antagonist and abatacept has been reported to be associated with an increased risk of infections including serious infections compared with TNF-antagonists alone, without increased clinical benefit. Therefore, the combination of REMIFLIX and abatacept is not recommended.

Concurrent administration with other biological therapeutics

There is insufficient information regarding the concomitant use of REMIFLIX with other biological therapeutics used to treat the same conditions as REMIFLIX. The concomitant use of REMIFLIX with these biologics 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 biologic to another, since overlapping biological activity may further increase the risk of 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. It is recommended that live vaccines not be given concurrently with REMIFLIX (see **section 4.3**).

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.

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).**

Infant exposure via breast milk

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

Autoimmune processes

The relative deficiency of TNFα caused by anti-TNF therapy may result in the initiation of an autoimmune process. It has been reported that treatment with REMIFLIX may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REMIFLIX and is positive for antibodies against double-stranded DNA, further treatment must not be given (see **section 4.8).** Patients who develop antidouble**-**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 REMIFLIX therapy.

Others

There is limited safety experience of REMIFLIX treatment in patients who have undergone surgical procedures, including arthroplasty. The long half-life of REMIFLIX should be taken into consideration if a surgical procedure is planned.

A patient who requires surgery while on REMIFLIX 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.

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.

Special populations

Elderly

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

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

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

REMIFLIX contains Sodium content

REMIFLIX contains 1,94 mg of sodium which is less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

Infliximab is however, diluted in sodium chloride 9 mg/mL (0,9 %) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet (see **section 6.1).**

Sucrose

REMIFLIX 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 REMIFLIX.

4.5 Interactions with other medicines and other forms of interaction

Use with anakinra or abatacept

An increased risk of serious infections was seen in clinical studies of other TNFα-blocking medicines used in combination with anakinra or abatacept, with no added clinical benefit. Because of the nature of the adverse reactions seen with these combinations with TNF-blocker therapy, similar toxicities may also result from the combination of anakinra or

abatacept with other TNFα-blocking medicines. Therefore, the combination of infliximab and anakinra or abatacept is not recommended. (see **section 4.4**)

Use with tocilizumab

The use of tocilizumab in combination with biological DMARDs such as TNFα antagonists, including REMIFLIX, should be avoided because of the possibility of increased immunosuppression and increased risk of infection.

Methotrexate (MTX) and other concomitant medications

Specific medicine interaction studies, including interactions with methotrexate (MTX), have not been reported. In rheumatoid arthritis, concomitant medications besides MTX were nonsteroidal anti-inflammatory medicines (NSAIDs), folic acid, corticosteroids and/or narcotics. Concomitant MTX use may decrease the incidence of anti-infliximab antibody production and increase infliximab concentrations.

Use with other therapeutics

The combination of REMIFLIX with other biological therapeutics used to treat the same conditions as REMIFLIX is not recommended (see **section 4.4**).

Serum infliximab concentrations appeared to be unaffected by baseline use of medications, including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates. It is recommended that live vaccines not be given concurrently with REMIFLIX. 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**).

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.

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

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g. TNFα, IL-1, IL-6, IL-10, IFN) during chronic inflammation. Therefore, it is expected that for a molecule that antagonises cytokine activity, such as infliximab, the formation of CYP450 enzymes could be normalised. Upon initiation or discontinuation of infliximab in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g. warfarin) or medicine concentration (e.g. cyclosporine or theophylline) is recommended and the individual dose of the medicine may be adjusted as needed.

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 REMIFLIX treatment to prevent pregnancy.

Pregnancy

The moderate number of prospectively collected pregnancies exposed to infliximab, as in REMIFLIX, resulting in live birth with known outcomes, including approximately 1100 exposed

during the first trimester, does not indicate an increase in the rate of malformation in the newborn.

Based on an observational study from northern Europe, an increased risk (OR, 95 % CI; p-value) for C-section (1,50, 1,14-1,96; p = 0,0032), preterm birth (1,48, 1,05-2,09; p = 0,024), small for gestational age (2,79, 1,54-5,04; p = 0,0007), and low birth weight (2,03, 1,41-2,94; p = 0,0002) was observed in women exposed during pregnancy to infliximab (with or without immunomodulators/corticosteroids, 270 pregnancies) as compared to women exposed to immunomodulators and/or corticosteroids only (6,460 pregnancies). The potential contribution of exposure to infliximab and/or the severity of the underlying disease in these outcomes remains unclear.

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

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

Infliximab crosses the placenta and has been detected in the serum of infants up to 12 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including serious disseminated infection that can become fatal. Administration of 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, as in REMIFLIX, 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 REMIFLIX on fertility and general reproductive function.

4.7 Effects on ability to drive and use machines

REMIFLIX may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of REMIFLIX (see **section 4.8**).

4.8 Undesirable effects

a) Summary of the safety profile

Most common adverse reactions (> 10 %) – infections (e.g. upper respiratory, sinusitis, and pharyngitis), infusion-related reactions, headache, and abdominal pain.

In the multi-centric, prospective, double-blind, comparator-controlled, parallel group clinical

study in patients with active Rheumatoid Arthritis (RA), on a stable dose of methotrexate. 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 below presents the side effects reported in patients treated with REMIFLIX. In the clinical study, 155 adverse events were reported. Out of 155 adverse events, 105 were reported in the REMIFLIX arm. There were nine subjects in the REMIFLIX arm who experienced at least one serious adverse event (SAE). There was no death reported in the study. Three subjects from the REMIFLIX arm experienced infusion related reactions and were discontinued.

Adverse reactions from clinical studies are listed below by system organ class and frequency grouping. Frequencies are defined as: 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.

MedDRA system organ class	**Frequency**	**Side effects**
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.
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	Common	Decreased appetite, dehydration, hypercholesterolaemia, hyperglycaemia, hypertriglyceridaemia.
	Uncommon	Dyslipidaemia.
Psychiatric disorders	Common	Depression, insomnia.
	Uncommon	Amnesia, agitation, confusion, somnolence, nervousness.
	Rare	Apathy.
Nervous system disorder	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 disorder	Common	Conjunctivitis (Eye irritation).
	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.
Hepato-biliary 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	Haematuria, nephrolithiasis, urinary incontinence.
	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.
Investigation	Common	Alanine aminotransferase increased, blood thyroid stimulating hormone increased, blood triglycerides increased, gamma-glutamyltransferase increase, hepatic enzyme increase, transaminases increase.
	Uncommon	Autoantibody positive.
	Rare	Complement factor abnormal.
Injury, poisoning, and procedural complications	Not known	Post-procedural complication (including infectious and non-infectious complications).

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

c) Description of selected adverse reaction

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.

Immunologic/infections

The most common infections reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Serious infections reported included pneumonia, cellulitis, abscess (skin, throat, and perirectal, intestinal, or perianal), sepsis, and bacterial infection. Opportunistic infections are reported like coccidioidomycosis, cryptococcosis, histoplasmosis, pneumocystosis, nocardiosis, and cytomegalovirus.

Constitutional symptoms (such as fever, chills, weight loss, and fatigue) may precede the onset of serious infections; however, signs or symptoms localised to the site of infection may also precede the majority of serious infections. Development of antibodies to infliximab, development of antinuclear antibodies complements factor abnormal, newly detected anti-dsDNA antibodies, moniliasis, lupus and lupus-like syndromes, listeriosis have been reported. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral (Herpes zoster, Herpes simplex), or parasitic organisms (including aspergillosis, blastomycosis, candidiasis,

coccidioidomycosis, legionellosis, listeriosis and tuberculosis) have been reported with TNF blockers. Listeria monocytogenes infections (with some cases resulting in death), other cases of tuberculosis (including miliary and disseminated) have been reported.

Inflammation and modulation of cellular immune response are mediated by TNF-α. It is possible that therapy with infliximab could affect normal immune responses. A meta-analysis has reported that there is evidence of an increased risk of serious infections in patients with rheumatoid arthritis treated with anti-TNF antibody therapy.

Infections have been observed in all organ systems and have been reported in patients receiving infliximab alone or in combination with immunosuppressive medicines.

Patients with antibodies to infliximab were more likely to have higher rates of clearance, reduced efficacy, and to experience an infusion reaction.

Various case reports regarding development of clinical symptoms of lupus-like syndrome have been reported in patients receiving infliximab therapy. However, symptoms resolved, and antibodies disappeared when infliximab was discontinued.

Respiratory

Most of the cases of tuberculosis have been reported within the first two months after the start of infliximab therapy and may reflect recrudescence of latent disease.

Respiratory side effects have included upper respiratory tract infections, coughing, epistaxis, lower respiratory tract infection (including pneumonia), pleural effusion, pleurisy, pulmonary oedema and shortness of breath. Interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis and very rare rapidly progressive disease) has been reported.

Hypersensitivity

Hypersensitivity side effects have included possible delayed hypersensitivity reaction,

generally reported as serum sickness or a combination of arthralgia and/or myalgia with fever and/or rash. Allergic reaction and allergic bronchopulmonary aspergillosis have been reported. Anaphylactic-like reactions (including laryngeal/pharyngeal oedema and severe bronchospasm, anaphylactic shock) have been associated with infliximab administration.

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).

Nervous system

Meningitis and sarcoidosis were also reported. Nervous system side effects have included headache, dizziness, vertigo, and syncope. Infliximab and other tumour necrosis factor blockers have been associated in rare cases with CNS manifestation of systemic vasculitis, seizures and new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disorders (including multiple sclerosis and optic neuritis), and peripheral demyelinating disorders (including Guillain-Barre syndrome). Hypoesthesia and paraesthesia have been commonly reported. Seizure associated with infliximab administration, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), transverse myelitis, and neuropathies have been reported.

Gastrointestinal

Gastrointestinal side effects have included nausea, abdominal pain, diarrhoea, dyspepsia, vomiting, constipation, gastrointestinal haemorrhage, blood in stool, gastroesophageal reflux, intestinal obstruction, intestinal perforation, intestinal stenosis, pancreatitis, diverticulitis, cheilitis and proctalgia.

Heart failure

Cardiovascular side effects have included higher incidences of mortality and hospitalisation due to worsening heart failure and trends towards increased dyspnoea, hypotension, angina, and dizziness in patients with moderate to severe heart failure. Cardiopulmonary reactions (primarily chest pain, hypotension, hypertension, or dyspnoea) or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions have accompanied infliximab infusions.

Hypertension, CHF, circulatory failure, hypotension, arrhythmia, bradycardia, cardiac arrest, tachycardia, myocardial infarction, thrombophlebitis, cyanosis, ecchymosis, peripheral ischaemia, petechiae, vasospasm, haematoma, palpitations and hot flush have been reported. Heart block has been reported during infliximab infusion. Pericardial effusion, vasculitis (systemic and cutaneous), worsening heart failure (with and without identifiable precipitating factors), and new onset heart failure (including heart failure in patients without known pre-existing cardiovascular disease) have been reported. Cases of myocardial ischaemia/infarction associated with infliximab administration (during or within 2 hours of infusion) have also been rarely reported.

A higher incidence of mortality and hospitalisation for worsening heart failure have been reported among patients with moderate to severe heart failure treated with the higher dose of innovator infliximab (10 mg/kg).

Dermatologic

Dermatologic side effects have included rash, pruritus, dry skin, cellulitis, increased sweating, ulceration, and granulomatous lesions, onychomycosis, seborrhoea, rosacea, skin papilloma, hyperkeratosis, worsening of symptoms of dermatomyositis, abnormal skin pigmentation. Furunculosis has been reported rarely.

Fungal dermatitis has been reported commonly. Psoriasis-like skin lesions have been associated with TNF-blockers. Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and new-onset and worsening psoriasis (all subtypes including pustular, primarily palmoplantar) have been reported. Bullous skin lesions and alopecia have also been reported.

Malignancies and lymphoproliferative disorders

Oncologic side effects have included malignancies (including lymphoma, non-melanoma skin

cancer, Merkel cell carcinoma. The majority of malignancies in chronic obstructive pulmonary disease (COPD) patients developed in the lung or head and neck. Other malignancies reported to occur with similar incidence to the general population, have included breast, colorectal, and melanoma. Cases of acute and chronic leukaemia have been reported with post-marketing TNF-blocker use in rheumatoid arthritis.

Malignancies (including non-Hodgkin's lymphoma and Hodgkin's disease) and lymphoproliferative disorders (including hepatosplenic T-cell lymphomas) have been reported. Patients with highly active disease and/or chronic exposure to immunosuppressants may be at a higher risk (up to several fold) than the population at large for the development of lymphoma.

Hepatobiliary events

Hepatic side effects have rarely included severe liver injury, including acute liver failure and autoimmune hepatitis. Reactivation of hepatitis B virus has been reported in patients who are chronic carriers of this virus (i.e. surface antigen positive). Hepatic function abnormal, elevated aminotransferases (ALT more common than AST), jaundice, cholestasis, cholecystitis, hepatocellular damage and hepatitis have been reported (see **section 4.4**). Severe hepatic reactions have occurred between weeks two to more than a year after initiation of innovator infliximab.

In general, patients who developed elevated ALT and AST were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of infliximab, or modification of concomitant medications.

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**).

Haematologic

Some cases of leucopenia, neutropenia, thrombocytopenia, and pancytopenia had a fatal outcome.

Haematologic side effects have included pancytopenia, thrombocytopenia, anaemia, haemolytic anaemia, leucopenia, lymphocytosis, lymphopenia, agranulocytosis, and lymphadenopathy.

Neutropenia, idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura have been reported.

Musculoskeletal

Back pain, arthralgia, swollen joints, bone fracture and myalgia.

Renal

Pyelonephritis.

Metabolic

Dehydration.

Local

Injection site reactions that were mainly erythema, pruritus, rash, and pain

Genital

Vaginitis.

Ocular

Keratitis, periorbital oedema, hordeolum, endophthalmitis, and conjunctivitis. Decreased vision, cases of transient visual loss associated with infliximab administration (during or within 2 hours of infusion) have also been rarely reported.

Psychiatric

Confusion, depression, insomnia, amnesia, agitation, somnolence, nervousness, and apathy.

Other

Other side effects have included infusion reactions, fatigue, fever, pain, oedema, impaired healing and influenza-like illness. Nonspecific symptoms (such as fever or chills) have been reported. Serious infusion related reactions (including anaphylaxis, convulsions, erythematous rash, and hypotension) were reported.

Serious infusion related reactions (symptoms included, but were not limited to, dyspnoea, urticaria, facial oedema, and hypotension) have also been reported following re-treatment

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 asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA websiteor to Cipla Medpro (Pty) Ltd. at e-mail: drugsafetysa@cipla.com or telephone 080 222 6662 (toll free).

4.9 Overdose

No case of overdose has been reported.

Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: L04AB02.

A.30.1 Biologicals- Antibodies

REMIFLIX 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 tumour necrosis factor (TNFα) but not to lymphotoxin α (TNFβ).

Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays.

Pharmacodynamic effects

Elevated concentrations of TNFα have been found in the joints of rheumatoid arthritis patients and correlate with elevated disease activity. Increased concentrations of TNFα have also been found in joint fluid/tissue and in psoriatic skin lesions in patients with psoriatic arthritis. In 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, chemo-attraction and tissue degradation. After infliximab treatment, patients exhibited decreased levels of serum interleukin 6 (IL-6) and C-reactive protein (CAP) compared to baseline. Peripheral blood lymphocytes further showed no significant decrease in number, or in proliferative responses to *in vitro* mitogenic stimulation when compared to untreated patients' cells. In psoriasis patients, treatment with infliximab resulted in decreases in epidermal inflammation and normalisation of keratinocyte differentiation in psoriatic plaques.

Elevated concentrations of TNFα have been found in the stools of Crohn's disease patients and correlate with elevated disease activity. Treatment with infliximab reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon

γ. After treatment with infliximab, patients with Crohn's disease have decreased levels of serum IL-6 and C-reactive protein compared to baseline. Peripheral blood lymphocytes from infliximab-treated patients however, showed no decrease in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients.

5.2 Pharmacokinetic properties

Single intravenous infusions of 1, 3, 5, 10 or 20 mg/kg of infliximab yielded dose proportional increases in the maximum serum concentration (C_{max}) and area under the concentration-time curve (AUC). The volume of distribution at steady state (median V_d of 3 to 4,1 litres) was not dependent on the administered dose and indicated that infliximab is predominantly distributed within the vascular compartment. No time-dependency of the pharmacokinetics was observed. The elimination pathways for infliximab have not been characterised.

No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight or hepatic or renal function. No notable differences in single dose pharmacokinetic parameters were observed between paediatric and adult Crohn's disease patients.

At single doses of 3, 5 and 10 mg/kg the median pharmacokinetic values for C_{max} were 0,077; 0,118 and 0,277 mg/mL respectively. The median terminal half-life at these doses ranged from 8 to 9,5 days. In most patients, infliximab could be detected in the serum for at least 8 weeks after a single infusion.

Following the 3-dose regimen, a slight accumulation of infliximab was observed in the serum after the second dose and no further clinically relevant accumulation thereafter. In most fistulising Crohn's disease patients, infliximab could be detected in serum for 12 weeks (range 4 to 28 weeks) after administration of the regimen.

Bioequivalence comparability clinical trial of REMIFLIX compared to commercially approved infliximab, Reference Manufactured Product (RMP) of innovator: A first-in-man, single-centre,

double-blind, randomized, single-dose, parallel-group study comparing the PK, safety and tolerability following 5 mg/kg IV infusion of REMIFLIX and RMP infliximab in healthy Caucasian male volunteers was conducted. The population comprised 84 patients, 43 evaluable patients receiving REMIFLIX and 41 patients receiving RMP infliximab. Following an IV infusion of 5 mg/kg over 2 hours, geometric mean C_{max} was 0,142 mg/mL following REMIFLIX versus 0,127 mg/mL following RMP infliximab geometric mean $AUC_{(0-t)}$ was 36,211 h.mg/mL versus 34,304 h.mg/mL and geometric mean $AUC_{(0-inf)}$ was 36,775 versus 34,801 h.mg/mL following REMIFLIX or RMP infliximab respectively.

Inter-subject variability was generally low for both products, with Coefficient of variation (CV) % of the order of 12-23 %. Infliximab terminal phase half-life, volume of distribution and clearance were similar across treatments. 90 % CIs for the treatment geometric mean ratios were 1,07 to 1,18; 0,98 to 1,14 and 0,98 to 1,15 for C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$, respectively. For the pre-defined primary PK parameters C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$, the determined confidence intervals for the treatment mean ratios were within the conventional limits of 0,80 to 1,25. Infliximab terminal phase half-life, volume of distribution and clearance were similar across treatments. It was concluded that PK Bioequivalence comparability was demonstrated between REMIFLIX and RMP infliximab.

5.3 Preclinical safety data

Single dose toxicity study

In a single dose toxicity study conducted in rats, infliximab was well tolerated up to a dose of 300 mg/kg body weight. The dose tested was 16 times the human approved clinical equivalent dose. In mouse, a maximum dose of 420 mg/kg body weight was tested and found to be safe. This dose was 11,4 times the human equivalent approved therapeutic dose.

Repeated dose studies in rats and rabbits by intravenous route:

In a rat study, three dose levels viz., 18,0; 72,0 and 144,0 mg/kg (low, mid, and high dose) were selected. In rabbits the doses were 9, 36 and 72 IU/kg body weight/day. The selected dose levels were 1, 4 and 8 times higher than the human equivalent dose (considering the dose of infliximab as 3,0 mg/kg). In both the studies, there was no mortality. None of the animals showed any treatment related clinical signs or behavioural changes. There were no treatment related changes in body weight or feed consumption. Clinical pathology, gross pathology, organ weight and histopathology did not reveal any treatment related adverse effect. The No Observed Adverse Effect Level (NOAEL) of infliximab when administered intravenously, twice a week for four weeks, to rats was 144 mg/kg and rabbits was 72 mg/kg. Both these doses were the highest doses tested.

Skin sensitisation

This study was conducted to assess the skin sensitisation potential of infliximab in guinea pigs. Fifteen Hartley strain guinea pigs were divided into 2 groups. The control group had 5 males and treatment group had 10 females. Undiluted REMIFLIX (infliximab) formulation was injected intradermally during induction exposure on Day 0 and a dose volume of 0,2 ml was administered topically during induction (on day 6) and challenge exposure (on day 21). Visual observation of skin following challenge exposure did not reveal any positive skin response at 24h and 48h post patch removal in the guinea pigs belonging to treatment group. To summarise, in acute study the treatment of infliximab did not reveal any toxic effect up to a dose of 300 mg/kg in rats and 420 mg/kg in mice. Repeated dose administered twice a week for four weeks intravenously in rats and rabbits did not reveal any toxicity up to a dose of 144 mg/kg and 72 mg/kg, respectively. These doses were the highest dose tested in each of the study. The doses were well above the equivalent human approved clinical dose of the

innovator product. Infliximab is not considered positive for skin sensitisation based on the study conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dibasic sodium phosphate dihydrate

Monobasic sodium phosphate monohydrate

Polysorbate 80

Sucrose

6.2 Incompatibilities

No physical biochemical compatibility studies have been conducted to evaluate the co-administration of REMIFLIX with other medicines.

REMIFLIX should not be infused concomitantly in the same intravenous line with other medicines.

6.3 Shelf life

Before reconstitution

The shelf life of REMIFLIX lyophilised vial is 36 months at (2 °C to 8 °C) from the date of manufacturing.

After reconstitution

In use stability of the reconstituted solution has been demonstrated for 24 hours at 25 °C. After reconstitution with water for injection the REMIFLIX may be stored refrigerated (2 °C to 8 °C) for up to 3 hours if not immediately used to prepare the dose for infusion. The intravenous infusion dose of REMIFLIX (infliximab) must be used within 3 hours of preparation.

6.4 Special precautions for storage

Unopened lyophilised powder: must be stored in the refrigerator at 2 ºC to 8 ºC.

For storage conditions up to 25°C before reconstitution of the REMIFLIX, see **section 6.3**.

For storage conditions after reconstitution and dilution of the REMIFLIX, see **section 6.3**.

Do not use REMIFLIX beyond the expiration date located on the carton and the vial.

Keep the vials in the outer carton until required for use.

6.5 Nature and contents of container

20 mL 20R glass vial made from Type I glass and bromobutyl rubber stopper and aluminium flip-off seal with white polypropylene flip-off cap, packed individually in a carton.

Each single dose vial contains 100 mg of infliximab for final reconstitution volume of 10 mL.

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.

REMIFLIX 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 REMIFLIX should begin within 3 hours of preparation.

The reconstituted infusion solution should be prepared by a trained medical professional using aseptic technique by the following procedure:

1. Calculate the required dose, total volume of reconstituted REMIFLIX solution required and the number of REMIFLIX vials needed. Each REMIFLIX vial contains 100 mg of the infliximab antibody.

2. Under aseptic conditions, reconstitute each REMIFLIX vial with 10 mL of sterile water for injection, using a syringe equipped with a 21-gauge (0,8 mm) or smaller needle as follows:
   - Remove the flip-top from the vial and wipe the top with an alcohol swab.
   - Insert the syringe needle into the vial through the centre of the rubber stopper and direct the stream of sterile water for injection, to the glass wall of the vial.
   - Gently swirl the solution by rotating the vial to dissolve the lyophilised powder.
   - Avoid prolonged or vigorous agitation. DO NOT SHAKE.
   - The solution for infusion should not be stored for more than 3 hours at 2 to 8 °C before use and should not be frozen.
   - Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes.
   - Following reconstitution with 10 mL of sterile water for injection, the solution should be colourless to straw coloured, clear to opalescent, free of visible particles.
   - The solution may develop a few translucent particles as (infliximab) is a protein. Do not use if the lyophilised cake has not fully dissolved or if opaque particles, discoloration, or other foreign particles are present.

3. Dilute the total volume of the reconstituted REMIFLIX solution dose to 250 mL with sterile 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 REMIFLIX solution from the 0,9 % *m/v* sodium chloride Injection, 250 mL glass bottle or bag.

Slowly add the total volume of reconstituted REMIFLIX solution to the 250 mL infusion bottle or bag. Gently mix. 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 REMIFLIX in the infusion bag only.

4. The REMIFLIX infusion 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. The vials do not contain antibacterial preservatives. 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 reuse. If reconstitution and dilution of REMIFLIX are performed under strict aseptic conditions, REMIFLIX 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 REMIFLIX with other medicines. REMIFLIX should not be infused concomitantly in the same intravenous line with other medicines.

6. REMIFLIX should be inspected visually before and after reconstitution for particulate matter and discoloration prior to administration, whenever solution and container

permit. If visibly opaque particles, discoloration, or other foreign particulates are observed, the solution should not be used.

7. Discard any unused portion of the infusion solution.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du Cap,

Mispel Street, Belville, 7530,

Customer Care: 080 222 6662

Manufacturer

Reliance Life Sciences Pvt. Ltd

DALC, Plant 2, R-282, TTC Area of MIDC,

Thane-Belapur Road, Rabale, Navi-Mumbai-400 701, India

8. REGISTRATION NUMBER(S)

53/30.1/0502

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 23 February 2021.

Latest renewal: To be allocated.

10. DATE OF REVISION OF THE TEXT

13 August 2026.