PROFESSIONAL INFORMATION (PI)

SCHEDULING STATUS

Schedule 4

1 NAME OF THE MEDICINE

REVELLEX® 100 mg powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of the REVELLEX product contains 100 mg of infliximab, a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology. After reconstitution, each mL contains 10 mg of infliximab.

Contains sugar (sucrose).

Each vial contains 500 mg sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

The powder is a freeze-dried white pellet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

REVELLEX is a "Disease-Controlling Anti-Rheumatic Therapy" (DCART) indicated for:

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

in patients with active disease despite treatment with methotrexate.

Safety and efficacy in rheumatoid arthritis have been demonstrated mainly with REVELLEX in combination with methotrexate.

Ankylosing spondylitis

REVELLEX is indicated for:

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

in patients with active disease.

Psoriatic arthritis

REVELLEX is indicated for:

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

in patients with psoriatic arthritis when the response to non-steroidal anti-inflammatory or disease modifying medicines has been inadequate. REVELLEX can be used with or without methotrexate.

Psoriasis

REVELLEX is indicated for:

- the reduction of signs and symptoms of psoriasis
- improvement in quality of life

in the treatment of adult patients with severe plaque psoriasis who are candidates for systemic therapy, and for patients with moderate psoriasis for whom phototherapy is inadequate or inappropriate.

Adult and paediatric Crohn's disease

REVELLEX is indicated for treatment of moderate to severe Crohn's disease for:

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

in patients who have an inadequate response to conventional therapies. REVELLEX therapy enables patients to reduce or eliminate corticosteroid use.

Fistulising Crohn's disease

REVELLEX is indicated for:

- the reduction in the number of draining enterocutaneous and rectovaginal fistulae and maintenance of fistula closure
- reduction of signs and symptoms
- improvement in quality of life

in patients with fistulising Crohn's disease.

Adult and paediatric ulcerative colitis

REVELLEX is indicated for:

- the reduction of signs and symptoms
- induction and maintenance of clinical remission
- induction of mucosal healing
- improvement in quality of life
- reduction or discontinuation of administration of corticosteroids
- reduction of ulcerative colitis-related hospitalisation

in patients with active ulcerative colitis who have had an inadequate response to conventional therapy.

4.2 Posology and method of administration

Posology

REVELLEX is administered by intravenous infusion.

REVELLEX 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, psoriasis or inflammatory bowel disease.

All patients administered REVELLEX intravenously are to be observed for at least 1 to 2 hours post infusion for side-effects. Medication, an artificial airway and other appropriate materials must be available for the treatment of these effects (see section 4.4).

Rheumatoid arthritis

Initially a 3 mg/kg given as an intravenous infusion is to be followed with additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

REVELLEX should be given in combination with methotrexate.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. If a patient has an inadequate response or loses response after this period, consideration may be given to increase the dose step-wise by approximately 1,5 mg/kg, up to a maximum of 7,5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be considered. If adequate response is achieved, patients should be continued on the selected dose or dose frequency. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment or after dose adjustment.

Ankylosing spondylitis

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

Psoriatic arthritis

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

Psoriasis

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

Moderate to Severe Crohn's disease in adults

For optimal long-term symptom control, 5 mg/kg given as a single intravenous infusion 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 have an incomplete response during maintenance treatment, consideration may be given to adjusting the dose up to 10 mg/kg.

Alternatively, an initial 5 mg/kg intravenous infusion administered may be followed by repeat infusions of 5 mg/kg when signs and symptoms of the disease recur; however, there is limited data on dosing intervals beyond 16 weeks.

Paediatric Crohn's disease

5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg.

Paediatric Crohn's disease patients who have had their dose adjusted to greater than 5 mg/kg every 8 weeks, may be at greater risk for adverse reactions. Continued therapy with the adjusted dose should be carefully considered in patients who show no evidence of additional therapeutic benefit after dose adjustment.

Fistulising Crohn's disease in adults

5 mg/kg intravenously, followed with additional 5 mg/kg doses administered at 2 and 6 weeks after the first infusion, for treatment of fistula(s) in Crohn's disease. If a patient does not respond after these 3 doses, no additional treatment with REVELLEX should be given.

The 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 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 disease recur is limited and comparative data on the benefit/risk of the alternative strategies for combined treatment are lacking.

Adult or Paediatric Ulcerative colitis

5 mg/kg given as an intravenous infusion, followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. For adult patients who have an incomplete response or lose their response, consideration may be given to treatment with 10 mg/kg.

Re-administration for Crohn's disease and rheumatoid arthritis

If signs and symptoms of disease recur, REVELLEX can be re-administered within 16 weeks following the last infusion. Re-administration of REVELLEX with a medicine-free interval of 2 to 4 years following a previous infusion has been associated with a delayed hypersensitivity reaction in 10 patients with Crohn's disease (see section 4.8). After a medicine-free interval of 16 weeks to 2 years, the risk of delayed hypersensitivity following

re-administration is not known. Therefore, after a medicine-free interval of 16 weeks, re-administration cannot be recommended.

Re-administration for ankylosing spondylitis

Data supporting re-administration, other than every 6 to 8 weeks, has not been established.

Re-administration for psoriatic arthritis

Data supporting re-administration, other than every 8 weeks, has not been established.

Re-administration for psoriasis

Data supporting re-administration, other than every 8 weeks, has not been established.

Re-administration for ulcerative colitis

Data supporting re-administration, other than every 8 weeks, has not been established.

Special populations

Paediatrics (6 – 17 years of age):

REVELLEX has not been studied in children with Crohn's disease or ulcerative colitis < 6 years of age. The pharmacokinetics of REVELLEX has been evaluated in paediatric patients with Crohn's disease and ulcerative colitis. The safety and effectiveness of REVELLEX in paediatric patients with Juvenile Rheumatoid Arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis have not been established.

Renal impairment

REVELLEX has not been studied in patients with renal impairment. No dose recommendations can be made.

Hepatic impairment

REVELLEX has not been studied in patients with hepatic impairment. No dose recommendations can be made.

Method of administration

REVELLEX should be administered intravenously over a 2 hour period. All patients administered REVELLEX are to be observed for at least 1-2 hours post-infusion for acute infusion-related reactions.

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

Shortened infusions across adult indications

In carefully selected adult patients who have tolerated at least 3 initial 2-hour infusions of REVELLEX (induction phase) and are receiving maintenance therapy, consideration may be given to administering subsequent infusions over a period of not less than 1 hour. If an infusion reaction occurs in association with a shortened infusion, a slower infusion rate may be considered for future infusions if treatment is to be continued. Shortened infusions at doses > 6 mg/kg have not been studied (see section 4.8).

For preparation and administration instructions, see section 6.6.

In order to improve the traceability of biological medicinal products, the trademark and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

4.3 Contraindications

REVELLEX is contraindicated in:

- Patients with a known hypersensitivity to the active substance, infliximab, or to any murine proteins, or to any of the excipients listed in section 6.1.

- Infections including tuberculosis: REVELLEX is contraindicated in patients with tuberculosis or other severe infections such as sepsis, abscesses, or opportunistic infections. Patients must be closely monitored for infections including tuberculosis before, during and after REVELLEX treatment, in accordance with local recommendations. Treatment with REVELLEX must not be continued if a patient develops serious infections or sepsis.

- In patients with moderate or severe heart failure (NYHA Class III/IV) (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Infections

Bacterial (including sepsis and pneumonia), mycobacterial [including tuberculosis (frequently disseminated or extrapulmonary at clinical presentation)], invasive fungal, viral and other opportunistic infections have been observed in patients receiving REVELLEX.

Some of these infections have been fatal.

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

Patients must be evaluated for opportunistic infections such as histoplasmosis, invasive fungal infections, listeriosis, legionellosis and Pneumocystis carinii pneumonia, prior to initiation of and while using REVELLEX. Patients who have clinically manifested infections should be fully treated for these conditions prior to treatment with REVELLEX.

Tuberculosis

Patients should be evaluated for tuberculosis risk factors (including close contact with a person with active tuberculosis) and tested for latent tuberculosis infection prior to treatment with REVELLEX. Tuberculin tests may yield false negative results, especially in patients who are severely ill or immunocompromised.

Treatment of latent tuberculosis infection should be initiated prior to therapy with REVELLEX.

Anti-tuberculosis therapy should be considered prior to initiation of REVELLEX in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Anti-tuberculosis therapy prior to initiating REVELLEX should also be considered in

patients who have several or highly significant risk factors for tuberculosis infection and have a negative test for latent tuberculosis.

The decision to initiate anti-tuberculosis therapy in these patients should only be made following consultation with a medical practitioner with expertise in the treatment of tuberculosis and taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy.

Cases of active tuberculosis have occurred in patients treated with REVELLEX during and after treatment for latent tuberculosis. Patients receiving REVELLEX should be monitored closely for signs and symptoms of active tuberculosis during and after treatment, including patients who tested negative for latent tuberculosis infection.

Invasive fungal infections

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 REVELLEX treatment should be carefully considered before initiation of REVELLEX therapy.

In patients treated with REVELLEX, an invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if they develop a serious systemic illness. Invasive fungal infections may present as disseminated rather than localised disease, and antigen and antibody testing may be negative in some patients with active infection. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed.

The decision to administer empiric antifungal therapy should be made, if feasible, in consultation with a medical practitioner with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of anti-fungal therapy.

Congestive Heart failure

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

Human antichimeric antibody (HACA) development

134 of the 199 Crohn's disease patients treated with REVELLEX were evaluated for HACA; 18 (13 %) were HACA-positive (the majority at low titer, ≤ 1:20). Patients who were HACA-positive were more likely to experience an infusion reaction. The incidence of positive HACA responses was lower amongst Crohn's disease patients receiving immunosuppressant therapies such as corticosteroids (10/99 (10 %) of these patients developed positive HACA responses) than amongst those not receiving these agents (8/35 (23 %) of these patients developed positive HACA responses).

Infusion related reactions/ Hypersensitivity reactions

To minimise the incidence of hypersensitivity reactions, including infusion reactions and serum sickness-like reactions, REVELLEX should be administered as regular maintenance therapy after an induction regimen at weeks 0, 2 and 6 (see section 4.2).

REVELLEX has been associated with hypersensitivity reactions that vary in their time of onset. Hypersensitivity reactions, which include urticaria, dyspnoea and/or bronchospasm, laryngeal oedema, pharyngeal oedema, and hypotension, have occurred during or within 2 hours of REVELLEX infusion.

However, in some cases, serum sickness-like reactions have been observed in Crohn's disease patients 1 to 14 days after REVELLEX therapy. Symptoms associated with

these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial oedema, and/or dysphagia. REVELLEX should be discontinued for severe reactions. Medications for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction.

Data from the ATTRACT trial indicates that prophylactic pre-treatment (paracetamol and/or antihistamines) of patients for infusion reactions reduced the occurrence of subsequent infusion reactions. The infusion rate may be slowed in order to decrease infusion reactions especially if infusion reactions have occurred previously.

Infusion reactions following re-administration of REVELLEX

In a psoriasis clinical trial, a 3-dose induction of REVELLEX after a period of no treatment resulted in a higher incidence of serious infusion reactions during the re-induction regimen (see section 4.8) than had been observed in rheumatoid arthritis, psoriasis and Crohn's disease trials in which a period of no medicine treatment was followed by regular maintenance therapy without re-induction.

In the case where REVELLEX maintenance therapy for psoriasis is interrupted, REVELLEX should be reinitiated as a single dose followed by maintenance therapy.

In general, the benefit-risk of re-administration of REVELLEX after a period of no-treatment, especially as a re-induction regimen at given weeks 0, 2 and 6, should be carefully considered.

Autoimmune processes

Treatment with REVELLEX may result in the formation of autoimmune antibodies and in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REVELLEX treatment should be discontinued.

Neurological events

REVELLEX and other medicines that inhibit TNFα have been associated with seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders including multiple sclerosis, and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome.

Medical practitioners should exercise caution in considering the use of REVELLEX in patients with these neurologic disorders and should consider discontinuation of REVELLEX if these disorders develop.

Hepatobiliary Events

Cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of REVELLEX. Isolated cases of liver failure resulting in liver transplantation or death have occurred. A causal relationship between REVELLEX and these events has not been established. 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 develops, REVELLEX should be discontinued, and a thorough investigation of the abnormality should be undertaken. Reactivation of hepatitis B virus has occurred in patients receiving REVELLEX who are chronic carriers of this virus (i.e. surface antigen positive).

Patients should be tested for Hepatitis B Virus (HBV) infection before initiating treatment with immunosuppressants, including REVELLEX. For patients who test positive for hepatitis B surface antigen, consultation with a medical practitioner with expertise in the treatment of hepatitis B is recommended.

Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of, during treatment with REVELLEX, and for several months following discontinuation of REVELLEX.

Malignancies

Lymphoma

In the controlled portions of clinical trials of all the TNF blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During clinical trials of REVELLEX in patients with rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, the incidence of lymphoma in REVELLEX-treated subjects was higher than expected in the general population, but the occurrence of lymphoma was rare.

Patients with Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy.

Paediatric malignancy

Postmarketing cases of malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) who received TNF-blocking medicines (initiation of therapy ≤ 18 years of age), including REVELLEX, to treat Juvenile Idiopathic Arthritis (JIA), Crohn's disease or other conditions. Approximately half the reports were lymphomas. The other cases represented a variety of different malignancies and included malignancies that are not usually observed in children and adolescents. Most of the patients were receiving concomitant immunosuppressants, such as methotrexate, azathioprine or 6-marcaptopurine. The role of TNF-blockers in the development of malignancies in children and adolescents remains unclear.

Hepatosplenic T-cell lymphoma

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

Cases of hepatosplenic T-cell lymphoma have also occurred in Crohn's disease and ulcerative colitis patients receiving azathioprine or 6-mercaptopurine who were not treated with REVELLEX. Before initiating or continuing REVELLEX therapy in a patient who is receiving an immunosuppressant such as azathioprine or 6-mercaptopurine, carefully assess the need for continuing the immunosuppressant therapy in light of the potential risks of concomitant therapy. The causal relationship of hepatosplenic T-cell lymphoma to REVELLEX therapy remains unclear.

Leukaemia

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

Non-lymphoma malignancy

In the controlled portions of some clinical trials with TNF-blocking agents, more cases of non-lymphoma malignancy have been observed among patients receiving a TNF-blocker compared with control patients. The rate of non-lymphoma malignancies among REVELLEX treated patients was similar to that expected in the general population, whereas the rate among control patients was lower than expected.

In an exploratory clinical trial evaluating the use of REVELLEX in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in REVELLEX treated patients compared with control patients. All patients had a history of heavy smoking.

Skin cancers

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

Cervical cancer

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

The potential role of REVELLEX therapy in the development of malignancies is not known. Caution should be exercised when considering TNF blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Concurrent administration of TNF-alpha inhibitor and anakinra

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNFα blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with combination of the etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNFα-blocking agents. Therefore, the combination of REVELLEX and anakinra is not recommended.

Concurrent administration of REVELLEX with abatacept

In clinical studies, concurrent administration of TNF-blocking agents and abatacept have been associated with an increased risk of infections including serious infections compared with TNF-blocking agents alone, without increased clinical benefit. Because of

the nature of the adverse events seen with the combination of TNF-blocking agents and abatacept therapy, the combination of REVELLEX and abatacept is not recommended.

Concurrent administration with other biological therapeutics

There is insufficient information regarding the concomitant use of REVELLEX with other biological therapeutics used to treat the same conditions as REVELLEX. The concomitant use of REVELLEX with these biologics is not recommended because of the possibility of an increased risk of infection.

Switching between biological therapeutics

When switching from one biologic to another, patients should continue to be monitored, since overlapping biological activity may further increase the risk of infection.

Haematologic reactions

There have been reports of pancytopaenia, leukopaenia, neutropaenia, and thrombocytopaenia in patients receiving TNF-blockers, including REVELLEX. Caution should be exercised in patients treated with REVELLEX who have a current or past history of significant cytopaenias.

Vaccinations

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

Live vaccines/Therapeutic infectious agents

In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live

vaccines. Use of live vaccines can result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with REVELLEX is not recommended.

Infant exposure in utero

Fatal outcome due to disseminated Bacille Calmette-Guérin (BCG) infection has been reported in an infant who received BCG vaccine after *in utero* exposure to REVELLEX. A twelve month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to REVELLEX, unless infliximab exposure was limited to the first trimester of if infant infliximab serum levels are undetectable. Administration of a live vaccine prior to 12 months of age might be considered if the benefit of the vaccination clearly outweighs the theoretical risk of administration of live vaccines to the infants (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 REVELLEX serum levels are undetectable (see section 4.6)

Therapeutic infectious agents

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

Non-live vaccines

In a subset of patients from the ASPIRE study, a similar proportion of patients in each treatment group mounted an effective 2-fold increase in titres to a polyvalent pneumococcal vaccine, indicating that REVELLEX did not interfere with T-cell dependent humoral immune responses.

Paediatric use

REVELLEX is indicated for reducing signs and symptoms and for inducing and maintaining clinical remission in paediatric patients who have moderately to severely active Crohn's disease. It should be noted that all paediatric patients in the Phase III trial (REACH) were required to be on a stable dose of 6-mercaptopurine, azathioprine, or methotrexate (see sections 4.4, 4.2 and 4.8).

REVELLEX is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and reducing or discontinuing corticosteroid use in paediatric patients with ulcerative colitis who have had an inadequate response to conventional therapy (see sections 4.1 and 4.8).

REVELLEX has not been studied in children with Crohn's disease or ulcerative colitis < 6 years of age.

Safety and effectiveness of REVELLEX in paediatric patients with Juvenile Rheumatoid Arthritis (JRA), ankylosing spondylitis, psoriatic arthritis and plaque psoriasis have not been established. Therefore, no recommendation on dosage and directions can be made. However, clinical trial side effects for JRA (ages 4 – 17 years) are discussed under section 4.8.

The pharmacokinetics of REVELLEX has been evaluated in paediatric patients with Crohn's disease and ulcerative colitis.

Geriatric use

Specific studies of REVELLEX in elderly patients have not been conducted. No major age-related differences in clearance or volume of distribution were observed in clinical studies. The incidence of serious infections in REVELLEX-treated patients 65 years and older was greater than those under 65 years of age. In addition, there is a greater incidence of infections in the elderly population in general, therefore, caution should be used in treating the elderly.

Biosimilar interchangeability

The safety and efficacy of alternating or switching between REVELLEX and products that are biosimilar but not deemed interchangeable to REVELLEX has not been established. Therefore, alternating or switching between REVELLEX and products that are biosimilar cannot be recommended.

Sucrose

REVELLEX contains sucrose. Patients with rare hereditary conditions such as fructose, intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not be administered REVELLEX. REVELLEX contains sucrose, which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Specific medicine interaction studies have not been conducted with REVELLEX.

Concurrent use of REVELLEX with other biological therapies

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

Live vaccines/Therapeutic infectious agents

It is recommended that live vaccines not be given concurrently with REVELLEX. It is also recommended that live vaccines not be given to infants after *in utero* exposure to REVELLEX for 12 months following birth, unless infliximab exposure was limited to the first trimester of if infant infliximab serum levels are undetectable. Administration of a live vaccine prior to 12 months of age might be considered if the benefit of the vaccination clearly outweighs the theoretical risk of administration of live vaccines to the infants (see section 4.4).

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

It is recommended that therapeutic infectious agents not be given concurrently with REVELLEX (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing age must use adequate contraception during treatment and for 6 months after the last treatment with REVELLEX to prevent pregnancy.

Pregnancy

Available observational studies in pregnant women exposed to REVELLEX showed no increased risk of major malformations among live births as compared to those exposed to non-biologics. However, findings on other birth outcomes were not consistent across the studies. In one study conducted in North America IBD pregnancy registry, REVELLEX exposure was not associated with increased rates of miscarriage/stillbirth, low birth weight, small for gestational age, or infant infection in the first year of life as compared to exposure to non-biologics. [Maternal exposure to REVELLEX, Maternal exposure to Non-biologics: 294, 515]. In another study in Northern Europe among IBD and non-IBD patients, exposure to REVELLEX in combination with immunosuppressants (mainly systemic corticosteroids and azathioprine), but not REVELLEX as monotherapy, was associated with increased rates of preterm birth, small for gestational age, low birth weight, and infant hospitalisation for infection compared with non-biologic systemic treatment [Live births with maternal exposure to REVELLEX. Live births with maternal exposure to Non-biologics: 270, 6460]. Both studies have potential for confounding (e.g. the concomitant use of other medications or treatments was not controlled, and disease severity was not assessed).

It is not known whether REVELLEX can affect reproductive potential.

Since REVELLEX does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with REVELLEX. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of the mouse TNFα. Doses of 10 to 15 mg/kg in

pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies.

As with other IgG antibodies, REVELLEX crosses the placenta. REVELLEX has been detected in the serum of infants up to 12 months following birth. The clinical significance of low serum levels in infliximab on the immune status in infants is unknown.

After *in utero* exposure to REVELLEX, infants may be at increased risk of infection, including disseminated infection that can become fatal (see section 4.4).

Lactation

REVELLEX has been detected at low levels in human milk and in infant serum 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. Limited data from published literature reported that infants exposed to infliximab through breast milk had no increase in rates of infection and developed normally. The consideration of REVELLEX use during breastfeeding should take into account the importance of the medicine to the mother and the health benefits of breastfeeding for the infant.

Fertility

The effect of REVELLEX on human fertility has not been evaluated.

4.7 Effects on ability to drive and use machines

REVELLEX is unlikely to produce an effect on the ability to drive or operate machinery; however, patients who are fatigued should be cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Clinical trial data

Upper respiratory tract infection was the most common adverse drug reaction (ADR) reported in clinical trials, occurring in 25,3 % of REVELLEX-treated patients compared with 16,5 % of control patients. The most serious ADRs associated with the use of TNF blockers that have been reported for REVELLEX include HBV reactivation, congestive heart failure, serious infections (including sepsis, opportunistic infections and tuberculosis), 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).

Table 1: Undesirable Effects in Clinical Trials

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

Infections and Infestations	*Very Common*: Viral infection (e.g. influenza, herpes virus infection). *Common*: Bacterial infections (e.g. cellulitis, abscess) *Uncommon*: Fungal infections (e.g. onychomycosis) *Rare:* Meningitis
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	*Rare*: Lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease
Blood and lymphatic disorders	*Common*: Neutropenia, leucopenia, anaemia, lymphadenopathy *Uncommon*: Thrombocytopenia, lymphopenia, lymphocytosis *Rare*: Haemolytic anaemia
Immune system disorders	*Common*: Allergic respiratory symptom *Uncommon*: Anaphylactic reaction, lupus-like syndrome, serum sickness or serum sickness-like reaction *Rare*: Anaphylactic shock, sarcoid-like reaction
Psychiatric disorders	*Common*: Depression, insomnia *Uncommon*: Amnesia, agitation, confusion, somnolence, nervousness *Rare*: Apathy
Nervous system disorders	*Very common*: Headache *Common*: Vertigo, dizziness, hypoaesthesia, paraesthesia *Uncommon*: Neuropathy
Eye disorders	*Common*: Conjunctivitis *Uncommon*: Keratitis, periorbital oedema, hordeolum

	Rare: Endophthalmitis
Cardiac disorders:	*Common*: Tachycardia, palpitation *Uncommon*: Cardiac failure (new onset or worsening), syncope, bradycardia *Rare*: Cyanosis, pericardial effusion
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
Gastrointestinal disorders	*Very common*: Abdominal pain, nausea *Common*: Gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastroesophageal reflux, constipation *Uncommon*: Intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis
Hepatobiliary system disorders	*Common*: Abnormal hepatic function, increased transaminases *Uncommon*: Cholecystitis
Skin and subcutaneous tissue disorders	*Common*: Urticaria, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia *Uncommon*: Bullous eruption, seborrhoea, rosacea, skin papilloma, hyperkeratosis, abnormal skin pigmentation

	Rare: Furunculosis *Not known*: Worsening of symptoms of dermatomyositis

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

Infusion-related reactions

An infusion-related reaction was defined in clinical studies as any adverse event occurring during an infusion or within 1 hour after infusion. In Phase 3 clinical studies, 18 % of REVELLEX-treated patients compared with 5 % of placebo-treated patients experienced an infusion-related reaction. Overall, a higher proportion of patients receiving REVELLEX 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 REVELLEX-treated patients who had an infusion reaction during the induction period, through week 6, 27 % experienced an infusion reaction during the maintenance period, week 7 through week 54. Of patients who did not have an infusion reaction during the induction period, 9 % experienced an infusion reaction during the maintenance period.

In a clinical study of patients with rheumatoid arthritis (ASPIRE), infusions were to be administered over 2 hours for the first 3 infusions. The duration of subsequent infusions could be shortened to not less than 40 minutes in patients who did not experience serious infusion reactions. In this trial, sixty six percent of the patients (686 out of 1 040) received at least one shortened infusion of 90 minutes or less and 44 % of the patients (454 out of 1 040) received at least one shortened infusion of 60 minutes or less. Of the REVELLEX-treated patients who received at least one shortened infusion, infusion-related reactions occurred in 15 % of patients and serious infusion reactions occurred in 0,4 % of patients.

In a clinical study of patients with Crohn's disease (SONIC), infusion-related reactions occurred in 16,6 % (27/163) of patients receiving infliximab monotherapy, 5 % (9/179) of patients receiving REVELLEX in combination with azathioprine (AZA), and 5,6% (9/161)

of patients receiving AZA monotherapy. One serious infusion reaction (< 1 %) occurred in a patient on REVELLEX monotherapy.

In post-marketing experience, cases of anaphylactic-like reactions including laryngeal/pharyngeal oedema and severe bronchospasm, and seizure have been associated with REVELLEX administration (see section 4.4).

Cases of transient visual loss occurring during or within 2 hours of REVELLEX infusion have been reported. Events (some fatal) of myocardial ischaemia/infarction and dysrhythmia have been reported, some in close temporal association with infusion of infliximab; cerebrovascular accidents have also been reported in close temporal association with infusion of REVELLEX.

Infusion reactions following re-administration of REVELLEX

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 REVELLEX (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, REVELLEX treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed hypersensitivity

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

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

In a 1-year clinical study with repeated infusions in patients with Crohn's disease (ACCENT I study), the incidence of serum sickness-like reactions was 2,4 %.

Immunogenicity

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

In clinical studies using single and multiple REVELLEX doses ranging from 1 to 20 mg/kg, antibodies to infliximab were detected in 14 % of patients with any immunosuppressant therapy, and in 24 % of patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, 8 % of patients developed antibodies to infliximab. In psoriatic arthritis

patients who received 5 mg/kg with and without methotrexate, antibodies occurred overall in 15 % of patients (antibodies occurred in 4 % of patients receiving methotrexate and in 26 % of patients not receiving methotrexate at baseline). In Crohn's disease patients who received maintenance treatment, antibodies to infliximab occurred overall in 3,3 % of patients receiving immunosuppressants and in 13,3 % of patients not receiving immunosuppressants. The antibody incidence was 2-3 fold higher for patients treated episodically. Due to methodological limitations, a negative assay did not exclude the presence of antibodies to REVELLEX. Some patients who developed high titres of antibodies to infliximab had evidence of reduced efficacy. In psoriasis patients treated with REVELLEX as a maintenance regimen in the absence of concomitant immunomodulators, approximately 28 % developed antibodies to infliximab (see section 4.4 “Infusion reactions and hypersensitivity”).

Infections

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

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

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

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

Malignancies and lymphoproliferative disorders

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

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

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

In an exploratory clinical study involving patients with moderate to severe COPD who were either current smokers or ex-smokers, 157 adult patients were treated with REVELLEX at doses similar to those used in rheumatoid arthritis and Crohn's disease. Nine of these patients developed malignancies, including 1 lymphoma. The median duration of follow-up was 0,8 years (incidence 5,7 % [95 % CI 2,65 %-10,6 %]. There was one reported malignancy amongst 77 control patients (median duration of follow-up

0,8 years; incidence 1,3 % [95 % CI 0,03 %-7,0 %]). The majority of the malignancies developed in the lung or head and neck.

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

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

Heart failure

In a Phase II study aimed at evaluating REVELLEX in congestive heart failure (CHF), higher incidence of mortality due to worsening of heart failure were seen in patients treated with REVELLEX, especially those treated with the higher dose of 10 mg/kg (i.e. twice the maximum approved dose). In this study 150 patients with NYHA Class III-IV CHF (left ventricular ejection fraction ≤ 35 %) were treated with 3 infusions of REVELLEX 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 38 weeks, 9 of 101 patients treated with REVELLEX (2 at 5 mg/kg and 7 at 10 mg/kg) died compared to one death among the 49 patients on placebo.

There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REVELLEX. There have also been post-marketing reports of new onset heart failure, including heart failure in patients

without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.

Hepatobiliary events

In clinical studies, mild or moderate elevations of ALT and AST have been observed in patients receiving REVELLEX without progression to severe hepatic injury. Elevations of ALT ≥ 5 x Upper Limit of Normal (ULN) have been observed (see Table 2). Elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving REVELLEX than in controls, both when REVELLEX was given as monotherapy and when it was used in combination with other immunosuppressive medicines.

Most aminotransferase abnormalities were transient; however, a small number of patients experienced more prolonged elevations. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of REVELLEX, or modification of concomitant therapy. In post-marketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving REVELLEX (see section 4.4).

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

Indication	Number of Patients[3]		Median Follow-up (wks)[4]		≥3 x ULN		≥5 x ULN	
	placebo	REVELLEX	placebo	REVELLEX	placebo	REVELLEX	placebo	REVELLEX
Rheumatoid arthritis[1]	375	1 087	58,1	58,3	3,2%	3,9%	0,8%	0,9%
Crohn's disease[2]	324	1 034	53,7	54,0	2,2%	4,9%	0,0%	1,5%
Paediatric Crohn's	N/A	139	N/A	53,0	N/A	4,4%	N/A	1,5%

disease								
Ulcerative colitis	242	482	30,1	30,8	1,2%	2,5%	0,4%	0,6%
Paediatric Ulcerative colitis	N/A	60	N/A	49,4	N/A	6,7%	N/A	1,7%
Ankylosing spondylitis	76	275	24,1	101,9	0,0%	9,5%	0,0%	3,6%
Psoriatic arthritis	98	191	18,1	39,1	0,0%	6,8%	0,0%	2,1%
Plaque Psoriasis	281	1 175	16,1	50,1	0,4%	7,7%	0,0%	3,4%

[1] Placebo patients received methotrexate while REVELLEX patients received both REVELLEX and methotrexate.

[2] Placebo patients in the 2 Phase III studies in Crohn's disease, ACCENT I and ACCENT II, received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patients who were randomised to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in the ALT analysis. In the Phase IIIb trial in Crohn's disease, SONIC, placebo patients received AZA 2,5 mg/kg/day as active control in addition to placebo infliximab infusions.

[3] Number of patients evaluated for ALT.

[4] Median follow-up is based on patients treated.

Antinuclear antibodies (ANA)/Anti-double-stranded DNA (dsDNA) antibodies

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

Paediatric population

Juvenile rheumatoid arthritis patients

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

Infusion reactions

Infusion reactions occurred in 35 % of patients with juvenile rheumatoid arthritis receiving 3 mg/kg compared with 17,5 % of patients receiving 6 mg/kg. In the 3 mg/kg REVELLEX 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 REVELLEX 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 REVELLEX 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 in the REACH study than in adult Crohn's disease patients: anaemia (10,7 %), blood in stool (9,7 %), leucopenia (8,7 %), flushing (8,7 %), viral infection (7,8 %), neutropenia (6,8 %), bacterial infection (5,8 %), and respiratory tract allergic reaction (5,8 %). In addition, bone fracture (6,8 %) was reported, however, a causal association has not been established. Other special considerations are discussed below.

Infusion-related reactions

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

Immunogenicity:

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

Infections

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

Paediatric ulcerative colitis patients

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

Infusion-related reactions:

Overall, 8 (13,3 %) of 60 treated patients experienced one or more infusion reactions, with 4 of 22 (18,2 %) in the q8 week and 3 of 23 (13,0 %) in the q12 week treatment maintenance group. No serious infusion reactions were reported. All infusion reactions were mild or moderate in intensity.

Immunogenicity

Antibodies to infliximab were detected in 4 (7,7 %) patients through week 54.

Infections

Infections were reported in 31 (51,7 %) of 60 treated patients in C0168T72 and 22 (36,7 %) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in C0168T72 was similar to that in the paediatric Crohn's disease study (REACH) but higher than the proportion in the adults ulcerative colitis studies (ACT 1 and ACT 2). The overall incidence of infections in C0168T72 was 13/22 (59 %) in the every 8 week maintenance treatment group and 14/23 (60,9 %) in the every 12 week maintenance treatment group. Upper respiratory tract infection (7/60 [12 %]) and pharyngitis (5/60 [8 %]) were the most frequently reported respiratory system infections. Serious infections were reported in 12 % (7/60) of all treated patients.

In this study, there were more patients in the 12 to 17 year age group than in the 6 to 11 year age group (45/60 [75,0 %]) versus 15/60 [25,0 %]). While the numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on safety events, there were higher proportions of patients with serious adverse events and discontinuation due to adverse events in the younger age group than in the older age group. While the proportion of patients with infections was also higher in the younger age group, for serious infections, the proportions were similar in the two age groups. Overall proportions of adverse events and infusion reactions were similar between the 6 to 11 and 12 to 17 year age groups.

Post marketing experience

Additional adverse events, some with fatal outcome, reported from worldwide postmarketing experience with REVELLEX are included in Table 3.

Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to REVELLEX exposure.

The most common serious adverse events reported in the post-marketing experience in children were infections (some fatal) including opportunistic infections and tuberculosis, infusion reactions and hypersensitivity reactions. Spontaneous serious adverse events in the post-marketing experience with REVELLEX in the paediatric population have included malignancies including lymphoma, transient hepatic enzyme abnormalities, lupus-like syndromes and positive auto-antibodies.

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

Table 3 Post-Marketing Reports

Blood and Lymphatic System Disorders	Agranulocytosis (including infants exposed *in utero* to REVELLEX), idiopathic thrombocytopenic purpura, pancytopaenia, thrombotic thrombocytopenic purpura
General Disorders and Administration Site Conditions	Anaphylactic reactions, anaphylactic shock, infusion-related reactions, serum sickness
Cardiac Disorders	Pericardial effusion, myocardial ischaemia/myocardial infarction (within 24 hours of initiation of infusion), dysrhythmia (within 24 hours of initiation of infusion)
Eye Disorders	Transient visual loss occurring during or within 2 hours of infusion
Immune System Disorders	Vasculitis
Neoplasm Benign and Malignant	Hepatosplenic T-cell Lymphoma (the vast majority in Crohn's disease and ulcerative colitis: primarily adolescents and young adults), paediatric malignancy, leukaemia, melanoma, Merkel cell carcinoma, cervical cancer
Nervous System Disorders	Central nervous system demyelinating disorders (such as multiple sclerosis and optic neuritis), peripheral

	demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), neuropathies, seizure, transverse myelitis, cerebrovascular accidents occurring within approximately 24 hours of initiation of infusion, orbital apex sydrome
Infections and Infestations	Opportunistic infections (such as aspergillosis, atypical mycobacteria, coccidioidomycosis, cryptococcosis, candidiasis, histoplasmosis, listeriosis, pneumocystosis, legionellosis), salmonellosis, sepsis, tuberculosis, protozoal infections, hepatitis B reactivation, and vaccine breakthrough infection (after *in utero* exposure to REVELLEX)*
Respiratory, Thoracic and Mediastinal Disorders	Interstitial lung disease, including pulmonary fibrosis/interstitial pneumonitis and rapidly progressive disease
Hepatobiliary System Disorders	Hepatocellular damage, hepatitis, jaundice, autoimmune hepatitis, and liver failure
Skin and Subcutaneous Tissue Disorders	Vasculitis (primarily cutaneous), psoriasis including new onset and pustular (primarily palmar/plantar), Stevens-Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, linear IgA bullous dermatosis (LABD), acute generalised exanthematous pustulosis (AGEP), lichenoid reactions

* including bovine tuberculosis (disseminated BCG infection), 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 "**6.04 Adverse Drug Reactions Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: L04AB02

Mechanism of action

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of tumour necrosis factor alpha (TNFα), but not to lymphotoxin α (TNFβ).

Pharmacodynamic effects

Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays. 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 lesion 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 (CRP) 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 studies

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 77, 118 and 277 µg/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.

5.5 Preclinical safety data

A repeat dose toxicity study was conducted in mice given cV1q anti-mouse TNFα to evaluate tumourigenicity. CV1q is an analogous antibody that inhibits the function of the TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly

for 6 months. The weekly dose of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumourigenicity in mice. No clastogenic or mutagenic effects of REVELLEX were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. The significance of these findings for human risk is unknown. It is not known whether REVELLEX can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dibasic sodium phosphate, monobasic sodium phosphate, polysorbate 80 and sucrose.

6.2 Incompatibilities

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

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store the lyophilised product under refrigeration at 2 to 8 °C. Do not use beyond the expiry date.

The lyophilised product may also be stored at temperatures up to a maximum of 30 °C for a single period of up to 6 months. A new expiration date (6 months from removal from refrigerated storage) should be written on the carton. This new expiration date should not exceed the original 36 months expiry date printed on the carton. Upon removal from refrigerated storage, REVELLEX must not be returned to refrigerated storage.

This product contains no preservative.

For storage conditions of the reconstituted medicinal product, see the section 6.6.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

REVELLEX is supplied as a lyophilised powder in individually-boxed single-use glass vials with rubber stoppers and aluminium crimps protected by plastic caps.

6.6 Special precautions for disposal and other handling

Preparation and Administration - USE ASEPTIC TECHNIQUE

REVELLEX vials do not contain antibacterial preservatives. Therefore, after reconstitution the administration of the solution for infusion should be started as soon as possible and within 3 hours of reconstitution and the vials should not be re-entered or stored. The diluent to be used for reconstitution is 10 mL of sterile water for injection. The total dose of the reconstituted product must be further diluted to 250 mL with 0,9 % sodium chloride injection. The infusion concentration should range between 0,4 and 4 mg/mL. The REVELLEX infusion should begin within 3 hours of preparation.

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

2. Reconstitute each REVELLEX vial with 10 mL of sterile water for injection, using a syringe equipped with a 21-gauge (0,8 mm) or smaller needle. Upon reconstitution, each mL of reconstituted solution contains 10 mg of infliximab. Remove flip-top from the vial and wipe the top with a 70 % alcohol swab. Insert the syringe needle into the vial through the centre of the rubber stopper and direct the stream of 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. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. Check that the solution is colourless to light yellow and opalescent. The solution may develop a few fine translucent particles, as infliximab is a protein. Do not use if opaque particles, discolouration or other foreign particles are present.

3. Dilute the total volume of the reconstituted REVELLEX solution to 250 mL with 0,9 % m/v sodium chloride solution for infusion. **Do not dilute the reconstituted REVELLEX solution with any other diluent**. The dilution can be accomplished by withdrawing a volume of 0,9 % m/v sodium chloride solution for infusion from the 250 mL glass bottle or infusion bag equal to the volume of the reconstituted REVELLEX. Slowly add the total volume of reconstituted REVELLEX solution to the 250 mL infusion bottle or bag. Gently mix.

4. For adult and paediatric patients, administer the infusion solution over a period of not less than 2 hours.

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

   Use only an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1,2 μm or less). Since no preservative is present, it is recommended that the administration of the solution for infusion be started as soon as possible and within 3 hours of reconstitution and dilution. Any unused portion of the infusion solution should not be stored for re-use. If reconstitution and dilution are performed under strict aseptic conditions, REVELLEX 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 REVELLEX with other medicines. REVELLEX should not be infused concomitantly in the same intravenous line with other medicines.

6. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. If visibly opaque particles, discolouration or other foreign particulates are observed, the solution should not be used.

7. Discard any unused portion of the solution.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

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