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SCHEDULING STATUS

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PROPRIETARY NAME AND DOSAGE FORM

REVELLEX® 100 mg

COMPOSITION

Each vial of the REVELLEX product contains 100 mg of infliximab. After reconstitution, each vial of REVELLEX contains 100 mg of infliximab in 10 mℓ.

Inactive ingredients include polysorbate, sodium phosphate and sucrose.

PHARMACOLOGICAL CLASSIFICATION

A.30.1 Biologicals – Antibodies.

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

Clinical Pharmacology

Pharmacodynamic properties: 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.

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 77, 118 and 277 µ/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 fistuli sing Crohn's disease patients, infliximab could be detected in serum for 12 weeks (range 4 to 28 weeks) after administration of the regimen.

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 drugs 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.

CONTRAINDICATIONS

REVELLEX should not be administered to patients with known hypersensitivity to murine proteins or to any other components of the product.

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.

REVELLEX is contraindicated in patients with moderate or severe heart failure (NYHA Class III/IV) (see “Warnings” and “Side Effects”).

WARNINGS AND SPECIAL PRECAUTIONS

Warnings

Immunosuppression

TNFα mediates inflammation and modulates cellular immune response therefore the possibility exists for anti-TNF therapies, including REVELLEX, to affect normal immune responses.

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 “Contraindications” and “Side-Effects”).

Malignancy/Infection

Patients with long duration of Crohn’s disease and chronic exposure to immunosuppressant therapies are more prone to develop lymphomas and infections. The risk of development of lymphoma associated with the use of REVELLEX is inconclusive.

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.

For patients who have resided in or travelled to regions where invasive fungal infections such as tuberculosis, histoplasmosis, coccidioidomycosis or blastomycosis are endemic, the benefits and

risks of REVELLEX treatment should be carefully considered before initiation or continuation of REVELLEX therapy. In at risk patients treated with REVELLEX, tuberculosis or an invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if they develop a serious systemic illness. Tuberculosis and invasive fungal infections may present as disseminated rather than localised disease, and antigen 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. (see “Special Precautions: Infections”).

There have been reports of active tuberculosis in patients receiving REVELLEX, including extrapulmonary tuberculosis, presenting as either local or disseminated disease.
Before starting treatment with REVELLEX, all patients must be evaluated for both active and inactive (“latent”) tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests i.e. tuberculin skin test and chest x-ray should be performed in all patients. Prescribers are reminded of the risk of false negative tuberculin skin test results especially in patients who are severely ill or immunocompromised. If active tuberculosis is diagnosed, REVELLEX treatment should not be initiated.

If inactive (“latent”) tuberculosis is diagnosed, prophylactic anti-tuberculosis therapy must be started before the initiation of REVELLEX. In this situation, the benefit/risk balance of REVELLEX therapy

should be very carefully considered. Patients must be monitored closely for infections, including miliary tuberculosis, while on and after treatment with REVELLEX (see "Special Precautions").

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

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).

Hypersensitivity

REVELLEX has been associated with hypersensitivity reactions including anaphylactic and anaphylactoid reactions. Urticaria, dyspnoea and hypotension have occurred in association with REVELLEX infusion. REVELLEX should be discontinued in the case of severe reactions. Some of these reactions have been reported as anaphylaxis. Medications (e.g. antihistamines, corticosteroids, adrenaline and/or paracetamol), an artificial airway and other appropriate materials for the treatment of these effects must be available for immediate use (see "Special Precautions").

Autoimmunity

REVELLEX therapy may result in the formation of autoimmune antibodies and rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REVELLEX and is positive for antibodies against double-stranded DNA, treatment should be discontinued (see "Side Effects: Antinuclear Antibodies (ANA)/Anti-double-stranded DNA (dsDNA) antibodies"). In clinical trials, patients who develop anti-double-stranded DNA (anti-dsDNA) and/or symptoms suggestive of a lupus-like syndrome have had resolution of symptoms and disappearance of the anti-dsDNA after discontinuation of REVELLEX therapy.

Special precautions

Infusion reactions and hypersensitivity

REVELLEX has been associated commonly with acute infusion effects and uncommonly with delayed hypersensitivity reaction. These differ in their time of onset. Therefore, all patients receiving REVELLEX should be observed for at least 1 to 2 hours post infusion for side effects.

Acute infusion reactions may develop immediately or within a few hours of infusion. If acute infusion reactions occur, the infusion must be interrupted immediately. Some of these effects have been described as anaphylaxis. Medications (e.g. antihistamines, corticosteroids, adrenaline and/or paracetamol), an artificial airway and other appropriate materials for the treatment of these effects must be available for immediate use. Patients may be pre-treated with e.g. antihistamines, hydrocortisone and/or paracetamol to prevent mild and transient effects (see "Warnings: Hypersensitivity").

Antibodies to REVELLEX may develop in some patients and have been associated with an increased frequency of infusion reactions. A low proportion of the infusion reactions were serious

allergic reactions. In Crohn's disease patients, an association between development of antibodies to REVELLEX and reduced duration of response has also been observed. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to REVELLEX 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 are not receiving immunosuppressants during REVELLEX treatment potentially are at greater risk of developing these antibodies. These antibodies cannot always be detected in serum samples. If serious reactions occur, symptomatic treatment must be given and further REVELLEX infusions must not be administered.

Patients who developed antibodies to REVELLEX were more likely to develop infusion-related reactions (see "Side Effects: Immunogenicity").

A delayed hypersensitivity reaction has been observed in a significant number of patients (25 % in 1 clinical trial) with Crohn's disease who were re-treated with REVELLEX following a 2 to 4 year period without REVELLEX treatment. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash within 12 days following re-treatment. Some patients 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. Advise patients to seek immediate medical advice if they experience any delayed adverse events (see "Side Effects: Delayed Hypersensitivity"). If patients are re-treated after a prolonged period, they should be closely monitored for signs and symptoms of delayed hypersensitivity (see "Warnings: Hypersensitivity").

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

Caution should be exercised when considering the use of REVELLEX therapy in patients with a chronic infection or a history of recurrent infection.

Opportunistic infections including tuberculosis and other infections such as sepsis and pneumonia have been reported in patients treated with REVELLEX (see “Side Effects”).

Patients must be evaluated for the risk of tuberculosis, including latent tuberculosis, prior to initiation of REVELLEX. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests i.e. tuberculin skin test and chest x-ray, should be performed in all patients. Prescribers are reminded of the risk of false negative tuberculin skin test results especially in patients who are severely ill or immunocompromised. Patients who have clinically manifested infections and/or abscesses should be treated for these conditions prior to treatment with REVELLEX. If active tuberculosis is diagnosed, REVELLEX therapy must not be initiated (see “Contraindications”). If latent tuberculosis is diagnosed, treatment must be initiated prior to treatment with REVELLEX, in accordance with local recommendations. Patients must be monitored closely for infections, including miliary tuberculosis, while on and after treatment with REVELLEX.

Use of anti-tuberculosis therapy should be considered before the initiation of REVELLEX 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 risk of anti-tuberculosis therapy.

Suppression of TNFα may also mask symptoms of infection such as fever. Treatment with REVELLEX must be discontinued if a patient develops a serious infection or sepsis. As the elimination of REVELLEX may take up to 6 months, close monitoring of the patients throughout this period is important.

Patients with fistulising Crohn's disease with acute suppurative fistulas should not initiate REVELLEX therapy until a source for possible infection, specifically abscess, has been excluded.

There is limited safety experience of surgical procedures in REVELLEX treated patients. A patient who requires surgery while on REVELLEX should be closely monitored for infections and appropriate actions should be taken.

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

Concurrent administration of REVELLEX inhibitor and anakinra

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

Vaccinations

No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving REVELLEX therapy. It is recommended that live vaccines not be given concurrently. 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.

Autoimmune processes

The relative deficiency of TNFα caused by REVELLEX therapy may result in the initiation of an autoimmune process in a subgroup of genetically susceptible patients. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REVELLEX and is positive for antibodies against double-stranded DNA, treatment should be discontinued (see “Side Effects”).

Neurological events

REVELLEX and other agents that inhibit TNFα have been associated with rare cases of optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disorders including multiple sclerosis (see “Side Effects”). A careful risk/benefit evaluation is recommended when prescribing REVELLEX to patients with pre-existing or recent onset of central nervous system demyelinating disorders.

Lymphomas

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 across all approved indications the incidence of lymphoma in REVELLEX-treated subjects was higher than expected in the general population, but the occurrence of lymphoma was rare.

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.

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.

Hepatosplenic T-cell lymphomas

Post-marketing cases of hepatosplenic T-cell lymphoma have been reported in adolescent and young adult patients with Crohn's disease treated with REVELLEX. This type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All cases of hepatosplenic T-cell lymphomas with REVELLEX have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine. Before initiating or continuing REVELLEX therapy in a patient who has chronic inflammatory bowel disease and who is receiving an immunosuppressant such as azathioprine or 6-mercaptopurine, the need for continuing the immunosuppressant therapy should be carefully assessed in light of the potential risks of concomitant therapy. No cases of hepatosplenic T-cell lymphoma have been identified in patients receiving REVELLEX alone. The causal relationship of hepatosplenic T-cell lymphoma to REVELLEX therapy remains unclear.

Heart failure

REVELLEX should be used with caution in patients with mild heart failure (NYHA Class I/II) (see "Contraindications" and "Side Effects").

Hepatobiliary Events

Very rare 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 $\geq$ 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 has occurred in patients receiving REVELLEX who are chronic carriers of this virus (i.e. surface antigen positive). Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of and during treatment with REVELLEX.

Others

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.

Geriatric use

No major differences were observed in the pharmacokinetics of REVELLEX in elderly (65 to 80 years) rheumatoid arthritis patients. The pharmacokinetics of REVELLEX in elderly Crohn's disease patients has not been studied.

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

Women of childbearing age

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

Paediatric patients

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 "Dosage and Administration", "Side Effects - Adverse Reactions in Paediatric Crohn's disease" and "Precautions – Vaccinations"). In addition 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.

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

Safety and effectiveness of REVELLEX in patients with juvenile rheumatoid arthritis has not been established.

INTERACTIONS

Medicine/Laboratory test interactions

In rheumatoid arthritis, psoriatic arthritis and Crohn's disease patients, the formation of antibodies to REVELLEX has been shown to be reduced when REVELLEX is administered concomitantly with methotrexate and other immunomodulators. No other information is available regarding possible effects of other immunosuppressive medicines or their effects on the pharmacokinetics of REVELLEX.

The combination of REVELLEX and anakinra is not recommended. See "Special Precautions: Concurrent administration of REVELLEX and anakinra."

PREGNANCY AND LACTATION

Safety during pregnancy and lactation has not been demonstrated.

DOSAGE AND DIRECTIONS FOR USE

For recommended infusion duration for patients for each of the indications described below, see section Preparation and Administration - USE ASEPTIC TECHNIQUE, point 4.

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 or inflammatory bowel disease.

All patients administered REVELLEX 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 "Warnings").

Rheumatoid arthritis

Initially a 3 mg/kg intravenous infusion (see "Preparation and Administration, point 4 " below) 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 (see "Preparation and Administration, point 4" below), 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, (see "Preparation and Administration, point 4" below), 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 (see "Preparation and Administration, point 4" below), 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 (see "Preparation and Administration, point 4 " 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 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. There is insufficient safety and efficacy data for use of REVELLEX beyond the recommended duration (see “Indications”).

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. REVELLEX should be administered with concomitant immunomodulators, including 6-mercaptopurine (6-MP), azathioprine (AZA) or methotrexate (MTX).

Fistulising Crohn’s disease in adults

5 mg/kg intravenously (see “Preparation and Administration, point 4” below), 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. There is insufficient safety and efficacy data for use of REVELLEX beyond the recommended duration (see “Indications”).

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 “Special Precautions”).

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 (see "Preparation and Administration, point 4" below), followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

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 "Side-Effects: Delayed Hypersensitivity"). 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, are not available at this time.

Re-administration for psoriatic arthritis

Data supporting re-administration, other than every 8 weeks, are not available at this time.

Re-administration for psoriasis

Data supporting re-administration, other than every 8 weeks, are not available at this time.

Re-administration for ulcerative colitis

Data supporting re-administration, other than every 8 weeks, are not available at this time.

Preparation and Administration - USE ASEPTIC TECHNIQUE

REVELLEX vials do not contain antibacterial preservatives. Therefore, after reconstitution the vials should be used immediately and not 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 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 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. 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, by withdrawing a volume of 0,9 % m/v sodium chloride injection, equal to the volume of reconstituted REVELLEX from the 0,9 % m/v sodium chloride injection 250 mℓ glass bottle or bag. 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 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 agents. REVELLEX should not be infused concomitantly in the same intravenous line with other agents.

6. Parenteral drug 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.

SIDE EFFECTS

In clinical trials with REVELLEX, adverse events (AE's) reasonably attributable to treatment were observed in approximately 40 % of placebo-treated patients and 60 % of REVELLEX-treated patients. Reasonably-related AE's are listed in **Table 1** by System Organ Class and frequency (common > 1/100, < 1/10; uncommon > 1/1 000, < 1/100; rare > 1/10 000, < 1/1 000). Frequency is based on the excess incidence of the AE compared with placebo in pooled data from clinical trials. Most AE's were mild to moderate in severity. Infusion-related reactions were the most common AE's reported. The most common causes for discontinuation of treatment were the infusion-related reactions: dyspnoea, urticaria and headache.

Table 1

Undesirable Effects in Clinical Trials

Infections and Infestations Common: Uncommon:	 Viral infection (e.g. influenza, herpes infections) Abscess, cellulitis, moniliasis, sepsis, bacterial infection, tuberculosis, fungal infection, hordeolum
Blood and lymphatic disorders Uncommon:	 Anaemia, leukopenia, lymphadenopathy, lymphocytosis, lymphopenia, neutropenia, thrombocytopenia, pancytopenia
Immune system disorders Common: Uncommon:	 Serum sickness-like reactions Lupus-like syndrome, respiratory tract allergic reaction (allergic rhinitis), anaphylactic reactions
Psychiatric disorders Uncommon:	 Depression, confusion, agitation, amnesia, apathy, nervousness, somnolence, insomnia
Nervous system disorders Common: Uncommon: Rare:	 Headache, vertigo/dizziness Exacerbation of demyelinating disease suggestive of multiple sclerosis Meningitis
Eye disorders Uncommon:	 Conjunctivitis, endophthalmitis, keratoconjunctivitis, periorbital oedema
Cardiac disorders: Uncommon:	 Syncope, bradycardia, palpitation, cyanosis, dysrrhythmia, worsening heart failure*

Rare:	Tachycardia
Vascular disorders Common: Uncommon: Rare:	 Flushing Ecchymosis/haematoma, hot flushes, hypertension, hypotension, petechia, thrombophlebitis, vasospasm, peripheral ischaemia Circulatory failure, systemic and cutaneous vasculitis, pericardial effusion
Respiratory thoracic and mediastinal disorders Common: Uncommon: Rare:	 Upper respiratory tract infection, lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, sinusitis Epistaxis, bronchospasm, pleurisy Pleural effusion
Gastrointestinal disorders Common: Uncommon: Rare:	 Nausea, diarrhoea, abdominal pain, dyspepsia Constipation, gastroesophageal reflux, cheilitis, diverticulitis Intestinal perforation, intestinal stenosis, gastro-intestinal haemorrhage
Hepatobiliary system disorders Uncommon: Rare:	 Abnormal hepatic function, cholecystitis Hepatitis
Skin and subcutaneous tissue disorders Common: Uncommon: 	 Rash, pruritus, urticaria, increased sweating, dry skin Fungal dermatitis/onychomycosis, eczema/seborrhoea, bullous eruption, furunculosis, hyperkeratosis, rosacea, verruca, abnormal skin pigmentation/colouring, alopecia

Musculoskeletal and connective tissue disorders Uncommon:	Myalgia, arthralgia, back pain
Renal and urinary system disorders Uncommon:	Urinary tract infection, pyelonephritis
Reproductive system and breast disorders Uncommon:	Vaginitis
General disorders and administration site conditions Common: Uncommon: Rare:	Fatigue, chest pain, infusion-related reactions, fever Injection site reactions, oedema, pain, chills/rigors, impaired healing Granulomatous lesion
Investigations Common: Uncommon:	Elevated hepatic transaminases Auto-antibodies, complement factor abnormality

* reported in early phase studies evaluating REVELLEX in patients with congestive heart failure

In post-marketing spontaneous reporting, infections were the most common serious adverse event. Some of the cases with infections or haematological adverse events have resulted in fatal outcomes. Cases of tuberculosis, sometimes fatal, including miliary tuberculosis and tuberculosis with extrapulmonary location (see “Special Precautions”) and other opportunistic infections, such as atypical mycobacteria, pneumocystis carinii pneumonia (PCP), histoplasmosis, coccidioidomycosis, cryptococcosis, aspergillosis, listeriosis, candidiasis and salmonellosis have been reported. In addition, central nervous system demyelinating disorders (such as multiple sclerosis and optic

neuritis), peripheral myelinating disorders (such as Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy), neuropathies, numbness, tingling, seizures, transverse myelitis, pancytopenia, haemolytic anaemia, idiopathic thrombocytopaenic purpura, thrombotic thrombocytic purpura, Stevens-Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, agranulocytosis, hepatocellular damage, hepatitis B reactivation, jaundice, autoimmune hepatitis, liver failure, pancreatitis, anaphylactic shock, interstitial pneumonitis/fibrosis, vasculitis psoriasis, including new onset and pustular (primarily palmar / plantar), pericardial effusion, and hepatosplenic T-cell lymphoma (primarily in adolescents and young adult patients with Crohn's disease) have been reported. Cases of transient visual loss and myocardial ischaemia / myocardial infarction occurring during or within 2 hours of REVELLEX infusion have also been reported.

In addition, interstitial lung disease (including pulmonary fibrosis / interstitial pneumonia) has been observed. Some of these cases have been reported to be rapidly progressive.

Heart failure In a Phase II study aimed at evaluating REVELLEX in moderate to severe 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. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors in patients taking REVELLEX. There have also been rare 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.

Infusion-related reactions Infusion-related reactions are more common in patients with antibodies to REVELLEX. An infusion-related reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 to 2 hours after an infusion. In clinical studies, approximately

20 % of infliximab-treated patients compared with approximately 10 % of placebo-treated patients experienced an infusion-related effect. Approximately 3 % of patients discontinued treatment due to infusions reactions, and all patients recovered with or without medical therapy.

Post-marketing surveillance has noted cases of transient visual loss and myocardial ischaemia / myocardial infarction occurring during or within 2 hours of REVELLEX infusion.

Delayed hypersensitivity In a clinical trial of 41 patients re-treated with REVELLEX following a 2 to 4 year period without REVELLEX treatment, 10 patients experienced undesirable effects manifesting 3 to 12 days following infusion. In 6 of these patients the effects were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash. Some patients also experienced pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and/or headache. The clinical data is not adequate to determine if the occurrence of these reactions were due to the different formulations administered to these patients in this study. Patients' signs and symptoms improved substantially or resolved with treatment in all cases. There are insufficient data on the incidence of these events after drug-free intervals of 1 to 2 years. These events have been observed only infrequently in clinical studies and post-marketing surveillance with re-treatment intervals up to 1 year. In the Phase III psoriasis study, 1 % of patients experienced symptoms of arthralgia, myalgia, fever and rash early in the treatment course following REVELLEX infusions.

Immunogenicity Patients who developed antibodies to REVELLEX were more likely (approximately 2 to 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 REVELLEX were detected in approximately 14 % of patients with any immunosuppressant therapy and in approximately 24 % of patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimen with methotrexate, approximately 8 % of patients developed antibodies to REVELLEX. Of Crohn's disease patients who received maintenance treatment, approximately 6 to 13 % developed antibodies to REVELLEX. The antibody incidence was 2 to 3 fold higher for patients treated episodically. Due to methodological shortcomings, a negative assay does not exclude the presence of antibodies to REVELLEX. Some patients who developed high titres of antibodies had evidence of reduced efficacy. In a Phase III psoriasis study, in which patients were treated with REVELLEX induction, followed by every 8 week maintenance infusions without concomitant immunosuppressive therapy, antibodies were detected in approximately 20 % of patients.

Infections In clinical trials, 35 % of REVELLEX-treated patients experienced infections compared with 22 % of placebo-treated patients. Serious infections e.g. pneumonia or abscesses were reported in 5 % of both REVELLEX-treated patients and placebo-treated patients. In a Phase III psoriasis study, after 24 weeks of follow-up, 1 % of REVELLEX-treated psoriasis patients compared to 0 % of placebo-treated patients developed serious infections.

Malignancies and lymphoproliferative disorders During clinical trials of REVELLEX, new or recurrent malignancies have been reported in REVELLEX-treated subjects. The incidence of lymphoma in REVELLEX-treated subjects was higher than expected in the general population (see "Special Precautions"). 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. The observed incidences of non-lymphoma malignancies were similar to what would be expected in the general population whereas the rate among control patients was lower than expected. In an exploratory clinical trial involving patients with moderate to severe chronic obstructive pulmonary disease (COPD), who were either current smokers or ex-smokers, more malignancies were reported in REVELLEX treated patients compared with control patients. The potential role of REVELLEX therapy in the development of malignancies is not known.

During post-marketing experience, a rare type of hepatosplenic T-cell lymphoma has been reported in adolescent and young adult patients with Crohn's disease treated with REVELLEX (see "Special Precautions").

Antinuclear antibodies (ANA)/Anti-double-stranded DNA (dsDNA) antibodies In clinical studies, approximately half of REVELLEX-treated patients who were ANA negative at baseline developed a positive ANA during the trial (compared with approximately one-fifth placebo-treated patients). Anti-dsDNA antibodies developed in approximately 17 % of patients treated with REVELLEX (compared with 0 % of placebo-treated patients). At the last evaluation 57 % of REVELLEX-treated patients remained, anti-dsDNA positive.

Clinical signs consistent with a lupus-like syndrome remain uncommon.

Hepatobiliary events In post-marketing surveillance, very rare cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving REVELLEX (see "Special Precautions"). A causal relationship between REVELLEX and these events has not been established.

In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REVELLEX without progression to severe hepatic injury. 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 agents. Most aminotransferase abnormalities were transient; however, a small number of patients experienced more prolonged elevations. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of REVELLEX, or modification of concomitant medications. ALT elevations ≥ 5 times the upper limit of normal was observed in 1 % of patients receiving REVELLEX.

Adverse Reactions in paediatric Crohn's disease

In general, the adverse events in paediatric patients who received REVELLEX were similar in frequency and type to those seen in adult Crohn's disease patients. Differences from adults and other special considerations are discussed in the following paragraphs.

The following adverse events were reported more commonly in 103 randomised paediatric Crohn's disease patients administered 5 mg/kg REVELLEX through 54 weeks, than in 385 adult Crohn's disease patients receiving a similar treatment regimen: anaemia (10,7 %), blood in stool (9,7 %), leukopenia (8,7 %), flushing (8,7 %), viral infection (7,8 %), neutropenia (6,8 %), bone fracture (6,8 %), bacterial infection (5,8 %) and respiratory tract allergic reaction (58 %).

Infections were reported in 56,3 % of randomised subjects in REACH and in 50,3 % of subjects receiving 5 mg/kg infliximab in ACCENT I. Within REACH, infections were reported more frequently for subjects who received every 8 week as opposed to every 12 week infusions (73,6 % and 38,0 %

respectively), while serious infections were reported for 3 subjects in the 8 week and 4 subjects in the 12 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. Pneumonia was reported in 3 patients, 2 in the 8 week and 1 in the 12 week maintenance treatment groups. Herpes zoster was reported in 2 patients in the 8 week maintenance treatment group.

Overall in REACH, 17,5 % of randomised patients experienced 1 or more infusion reactions, with 17,0 % and 18,0 % of patients in the 8 week and 12 week maintenance treatment groups, respectively. There were no serious infusion reactions and 2 subjects in REACH had non-serious anaphylactic reactions.

Antibodies to REVELLEX developed in 3 (2,9 %) paediatric patients.

Post-marketing Experience

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.

During post-marketing experience, a rare type of hepatosplenic T-cell lymphoma has been reported in adolescent and young adult patients with Crohn's disease treated with REVELLEX (see "Special Precautions - Lymphomas").

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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.

IDENTIFICATION

White solid with no evidence of meltback, free from foreign particles.

PRESENTATION

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

STORAGE INSTRUCTIONS

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 'Dosage and Directions for use' section.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

33/30.1/0531

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'n Afrikaanse voubiljet sal beskikbaar gemaak word op versoek.

An Afrikaans package insert will be made available on request.

Namibian Reg. No.: 05/4.4/0423

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