1. NAME OF THE MEDICINAL PRODUCT

Remsima 120 mg/ml S.C.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Remsima 120 mg/ml S.C. solution for subcutaneous injection in pre-filled pen
Each 1 mL single dose pre-filled pen contains 120 mg of infliximab*.

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

Excipient(s) with known effect
Sorbitol 45 mg per 1 mL

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection, subcutaneous.
Clear to opalescent, colourless to pale brown solution.

Patient safety information Card
The marketing of Remsima 120 mg/ml S.C. is subject to a risk management plan (RMP) including a 'Patient safety information card'.
The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

Remsima is a biosimilar medicinal product that has been demonstrated to be similar in quality, safety and efficacy to the reference medicinal product Remicade. Please be aware of any differences in the indications between the biosimilar medicinal product and the reference medicinal product. The biosimilar is not to be switched with the reference medicinal product unless specifically stated otherwise. More detailed information regarding biosimilar medicinal products is available on the website of the Ministry of Health:
https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/Registration/Pages/Biosimilars.aspx

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis:

Remsima, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:
• adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate.

• adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.
In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X ray, has been demonstrated.

4.2 Posology and method of administration

Remsima treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of conditions for which Remsima is indicated. Patients treated with Remsima should be given the package leaflet and the patient reminder card. Instruction for use is provided in the package leaflet.

For subsequent injections and after proper training in subcutaneous injection technique, patients may self-inject with Remsima if their physician determines that it is appropriate and with medical follow-up as necessary. Suitability of the patient for subcutaneous home use should be assessed and patients should be advised to inform their healthcare professional if they experience symptoms of an allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see section 4.4).

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

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous) is being administered to the patient, as prescribed. Remsima subcutaneous formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only.

Posology

Adults (≥18 years)

Rheumatoid arthritis
Treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 3 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks.

Remsima must be given concomitantly with methotrexate.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment (see section 5.1).

Re-administration for rheumatoid arthritis
From experience with intravenous infliximab, if the signs and symptoms of disease recur, infliximab can be re-administered within 16 weeks following the last administration. In clinical studies with intravenous infliximab, delayed hypersensitivity reactions have been uncommon and have occurred after infliximab-free intervals of less than 1 year (see sections 4.4 and 4.8). The safety and efficacy of re-administration after an infliximab-free interval of more than 16 weeks has not been established. This applies to rheumatoid arthritis patients.

In case maintenance therapy is interrupted, and there is a need to restart treatment, use of a re-induction regimen of intravenous infliximab is not recommended (see section 4.8). In this situation, infliximab should be re-initiated as a single dose of intravenous infliximab followed by the maintenance dose recommendations of subcutaneous infliximab described above given 4 weeks after the last administration of intravenous infliximab.

Switching to and from Remsima subcutaneous formulation
When switching from the maintenance therapy of infliximab intravenous formulation to the subcutaneous formulation of Remsima, the subcutaneous formulation may be administered 8 weeks after the last administration of Remsima 100 mg I.V.
There is insufficient information regarding the switching of patients who received Remsima 100 mg I.V. higher than 3 mg/kg for rheumatoid arthritis every 8 weeks to the subcutaneous formulation of Remsima.
Information regarding switching patients from the subcutaneous formulation to the intravenous formulation of Remsima is not available.

Missed dose
If patients miss an injection of Remsima subcutaneous formulation, they should be instructed to take the missed dose immediately in case this happens within 7 days from the missed dose, and then remain on their original bi-weekly dosing schedule. If the dose is delayed by 8 days or more, the patients should be instructed to skip the missed dose, wait until their next scheduled dose, and then remain on their original bi-weekly dosing schedule.

Special populations

Elderly

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

Renal and/or hepatic impairment

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

Paediatric population
Remsima is not indicated for children and adolescents under 18 years old.
The safety and efficacy of Remsima subcutaneous therapy in children aged below 18 years of age have not yet been established. No data are available.

Method of administration

Remsima 120 mg/ml S.C. solution for injection in pre-filled syringe or in pre-filled pen are administered by subcutaneous injection only. Full instructions for use are provided in the package leaflet. For the two initial intravenous infusions, patients may be pre-treated with, e.g., an antihistamine, hydrocortisone and/or paracetamol and infusion rate may be slowed in order to decrease the risk of infusion-related reactions especially if infusion-related reactions have occurred previously (see section 4.4). The physician should ensure appropriate follow-up of patients for any systemic injection reaction and localised injection site reaction after the initial subcutaneous injection is administered.

4.3 Contraindications

Hypersensitivity to the active substance, to other murine proteins or to any of the excipients listed in section 6.1.

Patients with tuberculosis or other severe infections such as sepsis, abscesses and opportunistic infections (see section 4.4).

Patients with moderate or severe heart failure (NYHA class III/IV) (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability

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

Systemic injection reaction/ localised injection site reaction/ hypersensitivity

Infliximab has been associated with systemic injection reactions, anaphylactic shock and delayed hypersensitivity reactions (see section 4.8).

Acute reactions including anaphylactic reactions may develop during (within seconds) or within a few hours following administration of infliximab. If acute reactions occur, medical treatment should be sought immediately. For this reason, the initial intravenous administrations should take place where emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway is immediately available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.

Localised injection site reactions predominantly of mild to moderate in nature included the following reactions limited to injection site: erythema, pain, pruritus, swelling, induration, bruising, haematoma, oedema, coldness, paraesthesia, haemorrhage, irritation, rash, ulcer, urticaria, application site vesicles and scab were reported to be associated with infliximab subcutaneous treatment. Most of these reactions may occur immediately or within 24 hours after subcutaneous injection. Most of these reactions resolved spontaneously without any treatment.

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

In clinical studies, delayed hypersensitivity reactions have been reported. Available data suggest an increased risk for delayed hypersensitivity with increasing infliximab free interval. Patients should be advised to seek immediate medical advice if they experience any delayed adverse reaction (see section 4.8). If patients are re-treated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.

Infections

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

Caution should be exercised when considering the use of infliximab in patients with chronic infection or a history of recurrent infections, including concomitant immunosuppressive therapy. Patients should be advised of and avoid exposure to potential risk factors for infection as appropriate.

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

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

Patients taking TNF-blockers are more susceptible to serious infections.

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

Patients who develop a new infection while undergoing treatment with infliximab, should be monitored closely and undergo a complete diagnostic evaluation. Administration of infliximab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

Tuberculosis

There have been reports of active tuberculosis in patients receiving infliximab. It should be noted that in the majority of these reports tuberculosis was extrapulmonary, presenting as either local or disseminated disease.

Before starting treatment with infliximab, 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, (e.g. tuberculin skin test, chest X-ray, and/or Interferon Gamma Release Assay), should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the patient reminder card. 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, infliximab therapy must not be initiated (see section 4.3).

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below, the benefit/risk balance of infliximab therapy should be very carefully considered.

If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with antituberculosis therapy before the initiation of infliximab, and in accordance with local recommendations.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, antituberculosis therapy should be considered before the initiation of infliximab.

Use of antituberculosis therapy should also be considered before the initiation of infliximab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

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

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

Invasive fungal infections

In patients treated with infliximab, an invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if they develop a serious systemic illness, and a physician with expertise in the diagnosis and treatment of invasive fungal infections should be consulted at an early stage when investigating these patients.

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

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

Hepatitis B (HBV) reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including infliximab, who are chronic carriers of this virus. Some cases have had fatal outcome.

Patients should be tested for HBV infection before initiating treatment with infliximab. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Carriers of HBV who require treatment with infliximab should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of treating patients who are carriers of HBV with antiviral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, infliximab should be stopped and effective antiviral therapy with appropriate supportive treatment should be initiated.

Hepatobiliary events

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

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 reactions seen with combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNFα-blocking agents. Therefore, the combination of infliximab and anakinra is not recommended.

Concurrent administration of TNF-alpha inhibitor and abatacept

In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of infliximab and abatacept is not recommended.

Concurrent administration with other biological therapeutics

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

Switching between biological DMARDs

Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse reactions, including infection.

Vaccinations

It is recommended that patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating Remsima therapy. Patients on infliximab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6).

In a subset of 90 adult patients with rheumatoid arthritis from the ASPIRE study a similar proportion of patients in each treatment group (methotrexate plus: placebo [n = 17], 3 mg/kg [n = 27] or 6 mg/kg infliximab [n = 46]) mounted an effective two-fold increase in titers to a polyvalent pneumococcal vaccine, indicating that infliximab did not interfere with T-cell independent humoral immune responses. However, studies from the published literature in various indications (e.g. rheumatoid arthritis, psoriasis, Crohn's disease) suggest that non-live vaccinations received during treatment with anti-TNF therapies, including infliximab may elicit a lower immune response than in patients not receiving anti-TNF 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 infliximab is not recommended.

Infant exposure *in utero*

In infants exposed *in utero* to infliximab, fatal outcome due to disseminated Bacillus Calmette-Guérin (BCG) infection has been reported following administration of BCG vaccine after birth. At least a six month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab (see section 4.6).

Infant exposure via breast milk

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

Therapeutic infectious agents

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder

instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with infliximab.

Autoimmune processes

The relative deficiency of TNFα caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with infliximab and is positive for antibodies against double-stranded DNA, further treatment with infliximab must not be given (see section 4.8).

Neurological events

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

Malignancies and lymphoproliferative disorders

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

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

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

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

Although subcutaneous administration is not indicated for children under age of 18 years, it should be noted that malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents (initiation of therapy ≤18 years of age), including infliximab in the post-marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in patients treated with TNF-blockers cannot be excluded.

Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF-blocking agents including infliximab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with AZA or

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

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

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

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

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

Heart failure

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

Haematologic reactions

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

Others

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

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

Special populations

Elderly

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

Sodium and sorbitol contents

Remsima contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free' and 45 mg sorbitol per 1 mL (in each 120 mg dose).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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

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

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

It is recommended that live vaccines not be given concurrently with infliximab. It is also recommended that live vaccines not be given to infants after *in utero* exposure to infliximab for at least 6 months following birth (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 sections 4.4 and 4.6).

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last infliximab treatment.

Pregnancy

The moderate number of prospectively collected pregnancies exposed to infliximab resulting in live birth with known outcomes, including approximately 1,100 exposed during the first trimester, does not indicate an increase in the rate of malformation in the newborn.

Based on an observational study from Northern Europe, an increased risk (OR, 95% CI; p-value) for C-section (1.50, 1.14-1.96; p = 0.0032), preterm birth (1.48, 1.05-2.09; p = 0.024), small for gestational age (2.79, 1.54-5.04; p = 0.0007), and low birth weight (2.03, 1.41-2.94; p = 0.0002) was observed in women exposed during pregnancy to infliximab (with or without immunomodulators/corticosteroids, 270 pregnancies) as compared to women exposed to

immunomodulators and/or corticosteroids only (6,460 pregnancies). The potential contribution of exposure to infliximab and/or the severity of the underlying disease in these outcomes remains unclear.

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

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

Infliximab crosses the placenta and has been detected in the serum of infants up to 6 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including serious disseminated infection that can become fatal. Administration of live vaccines (e.g. BCG vaccine) to infants exposed to infliximab *in utero* is not recommended for at least 6 months after birth (see sections 4.4 and 4.5). Cases of agranulocytosis have also been reported (see section 4.8).

Breast-feeding

Limited data from published literature indicate infliximab has been detected at low levels in human milk at concentrations up to 5% of the maternal serum level. Infliximab has also been detected in infant serum after exposure to infliximab via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Infliximab could be considered for use during breast-feeding.

Fertility

There are insufficient preclinical data to draw conclusions on the effects of infliximab on fertility and general reproductive function (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Upper respiratory tract infection was the most common adverse drug reaction (ADR) reported in clinical trials with infliximab, occurring in 25.3% of infliximab-treated patients compared with 16.5% of control patients. The most serious ADRs associated with the use of TNF blockers that have been reported for infliximab include HBV reactivation, CHF (congestive heart failure), serious infections (including sepsis, opportunistic infections and TB), serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, HSTCL, leukaemia, Merkel cell carcinoma, melanoma, sarcoidosis/sarcoid-like reaction, intestinal or perianal abscess (in Crohn's disease) and serious infusion reactions (see section 4.4).

The safety profile of Remsima subcutaneous formulation (evaluated in 168 and 175 patients for the subcutaneous infliximab group and the intravenous infliximab group, respectively) from active rheumatoid arthritis patients was overall similar to the safety profile of the intravenous formulation.

Tabulated list of adverse reactions

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

Table 1
Adverse reactions in clinical studies and from post-marketing experience of intravenous infliximab

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

Rare:	Transverse myelitis, central nervous system demyelinating disorders (multiple sclerosis-like disease and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy).
Not known:	Cerebrovascular accidents in close temporal association with infusion.
Eye disorders	
Common	Conjunctivitis
Uncommon	Keratitis, periorbital oedema, hordeolum
Rare	Endophthalmitis
Not known	Transient visual loss occurring during or within 2 hours of infusion
Cardiac disorders	
Common	Tachycardia, palpitation
Uncommon	Cardiac failure (new onset or worsening), arrhythmia, syncope, bradycardia
Rare	Cyanosis, pericardial effusion
Not known	Myocardial ischaemia/myocardial infarction
Vascular disorders	
Common	Hypotension, hypertension, ecchymosis, hot flush, flushing
Uncommon	Peripheral ischaemia, thrombophlebitis, haematoma
Rare	Circulatory failure, petechia, vasospasm
Respiratory, thoracic and mediastinal disorders	
Very common	Upper respiratory tract infection, sinusitis
Common	Lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, epistaxis
Uncommon	Pulmonary oedema, bronchospasm, pleurisy, pleural effusion
Rare	Interstitial lung disease (including rapidly progressive disease, lung fibrosis and pneumonitis)
Gastrointestinal disorders	
Very common:	Abdominal pain, nausea
Common:	Gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastroesophageal reflux, constipation
Uncommon	Intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis
Hepatobiliary disorders	
Common:	Hepatic function abnormal, transaminases increased.
Uncommon:	Hepatitis, hepatocellular damage, cholecystitis.
Rare:	Autoimmune hepatitis, jaundice.
Not known:	Liver failure.
Skin and subcutaneous tissue disorders	
Common:	New onset or worsening psoriasis including pustular psoriasis (primarily palm & soles), urticaria, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia.
Uncommon:	Bullous eruption, seborrhoea, rosacea, skin papilloma, hyperkeratosis, abnormal skin pigmentation.
Rare:	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, furunculosis, linear IgA bullous dermatosis (LABD), acute generalised exanthematous pustulosis (AGEP), lichenoid reactions.

Not known:	Worsening of symptoms of dermatomyositis.
Musculoskeletal and connective tissue disorders	
Common:	Arthralgia, myalgia, back pain.
Renal and urinary disorders	
Common:	Urinary tract infection.
Uncommon:	Pyelonephritis.
Reproductive system and breast disorders	
Uncommon:	Vaginitis.
General disorders and administration site conditions	
Very common:	Infusion-related reaction, pain.
Common:	Chest pain, fatigue, fever, injection site reaction, chills, oedema.
Uncommon:	Impaired healing.
Rare:	Granulomatous lesion.
Investigations	
Uncommon:	Autoantibody positive.
Rare:	Complement factor abnormal.

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

Description of selected adverse drug reactions

Systemic injection reaction and localised injection site reaction in adult patients administered with Remsima subcutaneous formulation

The safety profile of Remsima subcutaneous formulation in combination with methotrexate was evaluated in a Phase I/III parallel group study in patients with active rheumatoid arthritis. The safety population consisted of 168 patients in the Remsima subcutaneous group and 175 patients in the Remsima intravenous group. For study details, see Section 5.1.

The incidence rate of systemic injection reactions (e.g. rash, pruritus, flushing and oedema) was 1.2 patients per 100 patient-years in the Remsima subcutaneous group (from Week 6) and 2.1 patients per 100 patient-years in the Remsima intravenous group who switched to Remsima subcutaneous administration (from Week 30). All systemic injection reactions were mild to moderate.

The incidence rate of localised injection site reactions (e.g. injection site erythema, pain, pruritus and swelling) was 17.6 patients per 100 patient-years in the Remsima subcutaneous group (from Week 6) and 21.4 patients per 100 patient-years in those who switched to Remsima subcutaneous administration (from Week 30). Most of these reactions were mild to moderate and resolved spontaneously without any treatment within a day.

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

The incidence rate of localised injection site reactions (e.g. injection site erythema, pain, pruritus, bruising) was 23.3 patients per 100 patient-years in the Remsima subcutaneous group (from Week 6) and 7.5 patients per 100 patient-years in the Remsima intravenous group who switched to Remsima subcutaneous administration (from Week 30). All of these reactions were mild to moderate and mostly resolved spontaneously without any treatment within a few days.

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

Delayed hypersensitivity

In clinical studies delayed hypersensitivity reactions have been uncommon and have occurred after infliximab-free intervals of less than 1 year.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 infliximab-free intervals of more than 1 year but limited data from clinical studies suggest an increased risk for delayed hypersensitivity with increasing infliximab-free interval (see section 4.4).
Immunogenicity

Intravenous formulation

Patients who developed antibodies to infliximab were more likely (approximately 2-3 fold) to develop infusion-related reactions. Use of concomitant immunosuppressant agents appeared to reduce the frequency of infusion-related reactions.
In clinical studies using single and multiple infliximab doses ranging from 1 to 20 mg/kg, antibodies to infliximab were detected in 14% of patients with any immunosuppressant therapy, and in 24% of patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, 8% of patients developed antibodies to infliximab. In psoriatic arthritis patients who received 5 mg/kg with and without methotrexate, antibodies occurred overall in 15% of patients (antibodies occurred in 4% of patients receiving methotrexate and in 26% of patients not receiving methotrexate at baseline). In Crohn's disease patients who received maintenance treatment, antibodies to infliximab occurred overall in 3.3% of patients receiving immunosuppressants and in 13.3% of patients not receiving immunosuppressants. The antibody incidence was 2-3 fold higher for patients treated episodically. Due to methodological limitations, a negative assay did not exclude the presence of antibodies to infliximab. Some patients who developed high titres of antibodies to infliximab had evidence of reduced efficacy. In psoriasis patients treated with infliximab as a maintenance regimen in the absence of concomitant immunomodulators, approximately 28% developed antibodies to infliximab (see section 4.4: "Systemic injection reaction/ localised injection site reaction/ hypersensitivity").

Because immunogenicity analyses are assay-specific, comparison of the incidence of antibodies to infliximab reported in this section with the incidence of antibodies in other studies may be misleading.

Subcutaneous formulation

In rheumatoid arthritis patients on maintenance treatment, the incidence of anti-infliximab antibodies following the subcutaneous infliximab was demonstrated to be not higher than that of the intravenous infliximab and anti-infliximab antibodies had no significant impact on efficacy (determined by disease activity score in 28 joints [DAS28] and American College of Rheumatology criteria 20 [ACR20]) and the safety profile.

Infections

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

have been fatal; the most frequently reported opportunistic infections with a mortality rate of >5% include pneumocystosis, candidiasis, listeriosis and aspergillosis (see section 4.4).

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

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

In post-marketing spontaneous reporting, infections are the most common serious adverse reaction. 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 infliximab 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 infliximab 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 infliximab 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 infliximab with the vast majority of cases occurring in Crohn's disease and ulcerative colitis, and most of whom were adolescent or young adult males (see section 4.4).

Heart failure

In a Phase II study aimed at evaluating infliximab in CHF, higher incidence of mortality due to worsening of heart failure were seen in patients treated with infliximab, 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 infliximab 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 38 weeks, 9 of 101 patients treated with infliximab (2 at 5 mg/kg and 7 at 10 mg/kg) died compared to one death among the 49 patients on placebo.

There have been post-marketing reports of worsening heart failure, with and without identifiable

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

Hepatobiliary events

In clinical studies, mild or moderate elevations of ALT and AST have been observed in patients receiving infliximab without progression to severe hepatic injury. Elevations of ALT ≥5 x Upper Limit of Normal (ULN) have been observed (see Table 2). Elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving infliximab than in controls, both when infliximab was given as monotherapy and when it was used in combination with other immunosuppressive 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 infliximab, or modification of concomitant therapy. In post-marketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving infliximab (see section 4.4).

Table 2
Proportion of patients with increased ALT activity in clinical studies using intravenous infliximab

Indication	Number of patients[3]		Median follow-up (wks)[4]		≥ 3 x ULN		≥ 5 x ULN	
	placebo	infliximab	placebo	infliximab	placebo	infliximab	placebo	infliximab
Rheumatoid arthritis[1]	375	1,087	58.1	58.3	3.2%	3.9%	0.8%	0.9%

1 Placebo patients received methotrexate while infliximab patients received both infliximab and methotrexate.
2 Number of patients evaluated for ALT.
3 Median follow-up is based on patients treated.

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

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

Other special populations

Elderly

In rheumatoid arthritis clinical studies, the incidence of serious infections was greater in infliximab plus methotrexate-treated patients 65 years and older (11.3%) than in those under 65 years of age (4.6%). In patients treated with methotrexate alone, the incidence of serious infections was 5.2% in patients 65 years and older compared to 2.7% in patients under 65 (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form at https://sideeffects.health.gov.il.
In addition, you can report to Padagis via the following address: Padagis.co.il

4.9 Overdose

Single intravenous doses up to 20 mg/kg have been administered without toxic effects and repeated doses of Remsima subcutaneous formulation up to 240 mg have been administered without toxic effects. There is no specific treatment for Remsima overdose. In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Pharmacodynamic effects

Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays. Infliximab prevented disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα and when administered after disease onset, it allowed eroded joints to heal. *In vivo*, infliximab rapidly forms stable complexes with human TNFα, a process that parallels the loss of TNFα bioactivity.

Elevated concentrations of TNFα have been found in the joints of rheumatoid arthritis patients and correlate with elevated disease activity. In rheumatoid arthritis, treatment with infliximab reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion, chemoattraction and tissue degradation. After infliximab treatment, patients exhibited decreased levels of serum interleukin 6 (IL-6) and C-reactive protein (CRP), and increased haemoglobin levels in rheumatoid arthritis patients with reduced haemoglobin levels, compared with baseline. Peripheral blood lymphocytes further showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared with untreated patients' cells.

Clinical efficacy and safety

Adult rheumatoid arthritis

Intravenous formulation

The efficacy of infliximab intravenous formulation was assessed in two multicentre, randomised, double-blind, pivotal clinical studies: ATTRACT and ASPIRE. In both studies concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or non-steroidal anti-inflammatory drugs (NSAIDs) was permitted.

The primary endpoints were the reduction of signs and symptoms as assessed by the ACR criteria (ACR20 for ATTRACT, landmark ACR-N for ASPIRE), the prevention of structural joint damage, and the improvement in physical function. A reduction in signs and symptoms was defined to be at least a 20% improvement (ACR20) in both tender and swollen joint counts, and in 3 of the following 5 criteria: (1) evaluator's global assessment, (2) patient's global assessment, (3) functional/disability

measure, (4) visual analogue pain scale and (5) erythrocyte sedimentation rate or C-reactive protein. ACR-N uses the same criteria as the ACR20, calculated by taking the lowest percent improvement in swollen joint count, tender joint count, and the median of the remaining 5 components of the ACR response. Structural joint damage (erosions and joint space narrowing) in both hands and feet was measured by the change from baseline in the total van der Heijde-modified Sharp score (0-440). The Health Assessment Questionnaire (HAQ; scale 0-3) was used to measure patients' average change from baseline scores over time, in physical function.

The ATTRACT study evaluated responses at 30, 54 and 102 weeks in a placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with methotrexate. Approximately 50% of patients were in functional Class III. Patients received placebo, 3 mg/kg or 10 mg/kg infliximab at weeks 0, 2 and 6, and then every 4 or 8 weeks thereafter. All patients were on stable methotrexate doses (median 15 mg/wk) for 6 months prior to enrolment and were to remain on stable doses throughout the study.

Results from week 54 (ACR20, total van der Heijde-modified Sharp score and HAQ) are shown in Table 3. Higher degrees of clinical response (ACR50 and ACR70) were observed in all infliximab groups at 30 and 54 weeks compared with methotrexate alone.

A reduction in the rate of the progression of structural joint damage (erosions and joint space narrowing) was observed in all infliximab groups at 54 weeks (Table 3).

The effects observed at 54 weeks were maintained through 102 weeks. Due to a number of treatment withdrawals, the magnitude of the effect difference between infliximab and the methotrexate alone group cannot be defined.

Table 3
Effects on ACR20, Structural Joint Damage and Physical Function at week 54, ATTRACT

		Infliximab[b]				
	Control[a]	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks	All infliximab[b]
Patients with ACR20 response/Patients evaluated (%)	15/88 (17%)	36/86 (42%)	41/86 (48%)	51/87 (59%)	48/81 (59%)	176/340 (52%)
Total score[d] (van der Heijde-modified Sharp score)						
Change from baseline (Mean ± SD[c])	7.0±10.3	1.3 ± 6.0	1.6 ± 8.5	0.2 ± 3.6	-0.7 ± 3.8	0.6 ± 5.9
Median (Interquartile range)	4.0 (0.5,9.7)	0.5 (-1.5,3.0)	0.1 (-2.5,3.0)	0.5 (-1.5,2.0)	-0.5 (-3.0,1.5)	0.0 (-1.8,2.0)
Patients with no deterioration/patients evaluated (%)[c]	13/64 (20%)	34/71 (48%)	35/71 (49%)	37/77 (48%)	44/66 (67%)	150/285 (53%)
HAQ change from baseline over time[e] (patients evaluated)	87	86	85	87	81	339
Mean ± SD[c]	0.2 ± 0.3	0.4 ± 0.3	0.5 ± 0.4	0.5 ± 0.5	0.4 ± 0.4	0.4 ± 0.4

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

The ASPIRE study evaluated responses at 54 weeks in 1,004 methotrexate naive patients with early (≤3 years disease duration, median 0.6 years) active rheumatoid arthritis (median swollen and tender joint count of 19 and 31, respectively). All patients received methotrexate (optimised to 20 mg/wk by

week 8) and either placebo, 3 mg/kg or 6 mg/kg infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter. Results from week 54 are shown in Table 4.

After 54 weeks of treatment, both doses of infliximab + methotrexate resulted in statistically significantly greater improvement in signs and symptoms compared to methotrexate alone as measured by the proportion of patients achieving ACR20, 50 and 70 responses.

In ASPIRE, more than 90% of patients had at least two evaluable X-rays. Reduction in the rate of progression of structural damage was observed at weeks 30 and 54 in the infliximab + methotrexate groups compared to methotrexate alone.

Table 4
Effects on ACRn, Structural Joint Damage and Physical Function at week 54, ASPIRE

		Infliximab + MTX		
	Placebo + MTX	3 mg/kg	6 mg/kg	Combined
Subjects randomised	282	359	363	722
Percentage ACR improvement				
Mean ± SD[a]	24.8 ± 59.7	37.3 ± 52.8	42.0 ± 47.3	39.6 ± 50.1
Change from baseline in total van der Heijde-modified Sharp score[b]				
Mean ± SD[a]	3.70±9.61	0.42±5.82	0.51±5.55	0.46±5.68
Median	0.43	0.00	0.00	0.00
Improvement from baseline in HAQ averaged over time from week 30 to week 54[c]				
Mean ± SD[d]	0.68 ± 0.63	0.80 ± 0.65	0.88 ± 0.65	0.84 ± 0.65

a p <0.001, for each infliximab treatment group vs control
b greater values indicate more joint damage.
c HAQ = Health Assessment Questionnaire; greater values indicate less disability.
d p = 0.030 and <0.001 for the 3 mg/kg and 6 mg/kg treatment groups respectively vs. placebo + MTX.

Data to support dose titration in rheumatoid arthritis come from ATTRACT, ASPIRE and the START study. START was a randomised, multicentre, double-blind, 3-arm, parallel-group safety study. In one of the study arms (group 2, n=329), patients with an inadequate response were allowed to dose titrate with 1.5 mg/kg increments from 3 up to 9 mg/kg. The majority (67%) of these patients did not require any dose titration. Of the patients who required a dose titration, 80% achieved clinical response and the majority (64%) of these required only one adjustment of 1.5 mg/kg.

Subcutaneous formulation
The efficacy of subcutaneous infliximab in rheumatoid arthritis patients was assessed in a randomised, parallel-group pivotal Phase I/III study consisting of two parts: Part 1 to determine the optimal dose of subcutaneous infliximab and Part 2 to demonstrate non-inferiority in terms of efficacy of subcutaneous infliximab compared to intravenous infliximab treatment in a double-blind setting.

In Part 2 of this study, among 357 patients who were enrolled to receive 2 doses of Remsima 3 mg/kg intravenously at Weeks 0 and 2, 167 patients were randomised to receive Remsima 120 mg/ml S.C. subcutaneously at Week 6 and every 2 weeks up to Week 54, while 176 patients were randomised to receive Remsima 3 mg/kg intravenously at Weeks 6, 14 and 22 and then switched to Remsima 120 mg/ml S.C. subcutaneous at Week 30 once-every 2 weeks up to Week 54. Methotrexate was given concomitantly.

The primary endpoint of the study was the treatment difference of the change from baseline of DAS28 (CRP) at Week 22. The estimate of treatment difference was 0.27 with corresponding lower limit of the two-sided 95% confidence interval [CI] of 0.02 (95% CI: 0.02, 0.52), which was greater than the pre-specified non-inferiority margin of -0.6 indicating non-inferiority of Remsima subcutaneous formulation to Remsima intravenous formulation.

The analysis of other efficacy endpoints showed that efficacy profile of Remsima subcutaneous formulation compared to Remsima intravenous formulation in RA patients was generally comparable

in terms of disease activity measured by DAS28 (CRP and ESR) and ACR response up to Week 54. The mean scores for DAS28 (CRP) and DAS28 (ESR) gradually decreased from baseline at each time point until Week 54 in each treatment arm (see Table 5 and Table 6, respectively).

Table 5
Mean (SD) Actual Values of DAS28 (CRP and ESR)

	DAS28 (CRP)		DAS28 (ESR)	
Visit	**Remsima IV 3 mg/kg[b] (N=174)**	**Remsima SC 120 mg (N=165)**	**Remsima IV 3 mg/kg[b] (N=174)**	**Remsima SC 120 mg (N=165)**
Baseline	5.9 (0.8)	6.0 (0.8)	6.6 (0.8)	6.7 (0.8)
Week 6	4.1 (1.2)	4.0 (1.2)	4.8 (1.3)	4.6 (1.2)
Week 22	3.5 (1.2)[a]	3.3 (1.1)[a]	4.1 (1.3)	4.0 (1.1)
Week 54	2.9 (1.2)[b]	2.8 (1.1)	3.4 (1.3)[b]	3.4 (1.2)

a Two-sided 95% CI for difference in the mean change from baseline for DAS28 (CRP) at Week 22 was well above the pre-defined non-inferiority margin of -0.6
b Remsima IV was switched to Remsima SC at Week 30

Table 6
Proportions of Patients Achieving Clinical Response According to the ACR Criteria

	ACR20		ACR50		ACR70	
Visit	**Remsima IV 3 mg/kg[a] (N=174)**	**Remsima SC 120 mg (N=165)**	**Remsima IV 3 mg/kg[a] (N=174)**	**Remsima SC 120 mg (N=165)**	**Remsima IV 3 mg/kg[a] (N=174)**	**Remsima SC 120 mg (N=165)**
Week 6	103 (59.2%)	107 (64.8%)	45 (25.9%)	47 (28.5%)	18 (10.3%)	19 (11.5%)
Week 22	137 (78.7%)	139 (84.2%)	90 (51.7%)	85 (51.5%)	49 (28.2%)	46 (27.9%)
Week 54	125 (71.8%)[a]	132 (80.0%)	101 (58.0%) [a]	108 (65.5%)	68 (39.1%) [a]	77 (46.7%)

a Remsima IV was switched to Remsima SC at Week 30

5.2 Pharmacokinetic properties

Absorption and distribution

Single subcutaneous injections of 120, 180 and 240 mg of infliximab yielded approximately dose proportional increases in the maximum serum concentration (C_{max}) and area under the concentration time curve (AUC). The apparent volume of distribution during the terminal phase (mean of 7.3 to 8.8 litres) was not dependent on the administered dose.

After single doses of 120, 180 and 240 mg of subcutaneous infliximab administered to healthy subjects, the mean C_{max} values were 10.0, 15.1 and 23.1 µg/mL, respectively, and for all doses infliximab could be detected in the serum for at least 12 weeks thereafter.

The bioavailability of subcutaneous infliximab, estimated in a population PK model, was 58% (95% CI: 54% - 62%).

After administration of infliximab 120 mg subcutaneously every 2 weeks (from Week 6 after 2 doses of intravenous infliximab at Weeks 0 and 2) to patients with active rheumatoid arthritis who were

concomitantly treated with MTX, the median (CV%) C_{trough} level at Week 22 (steady state) was 12.8 μg/mL (80.1%).

Based on PK results from clinical studies in patients with active rheumatoid arthritis and population PK modelling, C_{trough} levels at steady state would be higher after administration of infliximab 120 mg subcutaneous formulation given every 2 weeks compared with infliximab 5 mg/kg intravenous formulation given every 8 weeks.

Elimination

The elimination pathways for infliximab have not been characterised. Unchanged infliximab was not detected in urine. No major age- or weight-related differences in clearance or volume of distribution were observed in rheumatoid arthritis patients.

In studies in healthy subjects, the mean (± SD) apparent clearance of Remsima 120 mg/ml S.C. administered subcutaneously was 19.3 ± 6.9 mL/hr.

In the RA patients, the mean (± SD) apparent clearance of Remsima 120 mg/ml S.C. subcutaneous at steady state was 18.8 ± 8.3 mL/hr.

The mean terminal half-life ranged from 11.3 days to 13.7 days for 120, 180 and 240 mg of subcutaneous infliximab administered to healthy subjects.

Special populations

Elderly

The pharmacokinetics of infliximab injected via subcutaneous route in elderly patients has not been studied.

Hepatic and renal impairment

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

5.3 Preclinical safety data

Infliximab does not cross react with TNFα from species other than human and chimpanzees. Therefore, conventional preclinical safety data with infliximab are limited. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. In a fertility and general reproductive function study, the number of pregnant mice was reduced following administration of the same analogous antibody. It is not known whether this finding was due to effects on the males and/or the females. In a 6-month repeated dose toxicity study in mice, using the same analogous antibody against mouse TNFα, crystalline deposits were observed on the lens capsule of some of the treated male mice. No specific ophthalmologic examinations have been performed in patients to investigate the relevance of this finding for humans.

Long-term studies have not been performed to evaluate the carcinogenic potential of infliximab. Studies in mice deficient in TNFα demonstrated no increase in tumours when challenged with known tumour initiators and/or promoters.

The subcutaneous administration of Remsima to New Zealand White rabbits was well tolerated at the actual concentration to be used in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol
Sodium acetate trihydrate
Polysorbate 80
Acetic acid
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

The expire date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze. Keep the medicinal product in its outer carton in order to protect from light.
The medicinal product may also be stored at temperatures up to a maximum of 25°C for a single period of up to 28 days. The medicinal product must be discarded if not used within the 28-day period.

6.5 Nature and contents of container

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

Packs of:

- 1 prefilled syringe with automatic needle guard (1 mL sterile solution) with 2 alcohol pads.
- 2 prefilled syringes with automatic needle guard (1 mL sterile solution) with 2 alcohol pads.
- 4 prefilled syringes with automatic needle guard (1 mL sterile solution) with 4 alcohol pads.

Remsima 120 mg/ml S.C. solution for subcutaneous injection in pre-filled pen
Remsima 120 mg/ml S.C. solution for subcutaneous injection in single-use pre-filled pen. The syringe inside the pen is made from type 1 glass with a plunger stopper (flurotec-coated elastomer) and needle with a rigid needle shield.

Packs of:

- 1 prefilled pen (1 mL sterile solution) with 2 alcohol pads.
- 2 prefilled pens (1 mL sterile solution) with 2 alcohol pads.
- 4 prefilled pens (1 mL sterile solution) with 4 alcohol pads.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Remsima is a solution that is clear to opalescent, colourless to pale brown. Do not use if the solution is cloudy, discoloured or contains visible particulate matter.

After use, place the pre-filled syringe with automatic needle guard/ pre-filled pen into a puncture resistant container and discard as required by local regulations. Do not recycle the injecting device. Always keep the medicinal product out of the sight and reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Registration Holder

Padagis Israel Agencies Ltd.
1 Rakefet St., Shoham, Israel

8. Manufacturer

Celltrion Inc.
Yeonsu-gu, Incheon, South Korea

9. Registration number

167-27-36349

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12.5.2022