REMSIMA™

- **Hepatitis B virus (HBV) reactivation**

  Prevention:
  Treatment with TNF blockers such as infliximab may result in reactivation of hepatitis B virus, in patients who carry this virus, which can be life-threatening in some cases. Patients should be tested for HBV infection before initiating treatment with infliximab.

  Monitoring:
  Carriers of HBV who require treatment with infliximab should be closely monitored for signs and symptoms of HBV reactivation infection throughout therapy and for several months following termination of therapy. Symptoms of HBV reactivation can consist of a sequential increase in HBV replication; appearance of hepatic injury and recovery signs. Most importantly, there should be a wider awareness about this condition, which could also have subclinical expression and spontaneous resolution.

  Measures:
  In patients who develop HBV reactivation, infliximab treatment should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

- **Hepatobiliary events**

  Prevention:
  Very rare cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of infliximab. The possible occurrence of this condition should be taken into consideration when starting the treatment with infliximab.

  Monitoring:
  Patients, treated with infliximab with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury (see also HBV reactivation). In general, patients who developed alanine transaminase (ALT) and aspartate transaminase (AST) elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of infliximab, or modification of concomitant therapy.

  Measures:
  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.

- **Intestinal and perianal abscess (in Crohn's disease)**

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

  Monitoring:
  Regular physical examination, including search for anamnestic data suggesting the occurrence of fistulae should be carried out in patients treated with infliximab.

  Measures:
  Discontinuation of infliximab should be considered if this condition develops during the treatment. Appropriate surgical procedures should be undertaken.

- **Systemic lupus erythematosus/lupus-like syndrome**

  Prevention:
  The relative deficiency of TNFα caused by anti-TNF therapy may result in the initiation of an autoimmune process.

  Monitoring:
  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. Symptoms can consist of joint pain or a rash on cheeks or arms that is sensitive to the sun.

  Measures:
  The treatment with infliximab should be discontinued. Symptomatic treatment for the pain and rash should be given, including for example anti-inflammatory agents, local corticosteroids etc.

- **Sarcoidiosis/sarcoid-like reactions**

  Prevention:
  If a patient develops symptoms suggestive of a sarcoid-like reaction (though observed very rarely in patients treated with infliximab), further treatment with infliximab must not be given.

  Monitoring:
  The patients treated with infliximab should be monitored for the occurrence of signs and symptoms suggesting the development of sarcoidosis or sarcoid-like reaction (mainly appearing as dyspnoea or cough, but sometimes as skin rashes, etc.)

  Measures:
  The treatment with infliximab should be discontinued. Appropriate symptomatic treatment should be undertaken, including for example bronchodilators, mucolytic agents, antibiotics etc.

Reference

1. Remsima™ (Infliximab), Summary of Product Characteristics, 2013.

Patient Alert Card

Patient Alert Card

Remsima™
Infliximab

Show this card to any doctor involved in your treatment.

Infusion Scheduler

- **Infusion scheduler for 8-weekly treatment from the 3rd cycle**

Infusion Card
8 Weekly Treatment
Remsima™

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get.

- **Infusion scheduler for 6-8 weekly treatment from the 3rd cycle (for patients with ankylosing spondylitis)**

Infusion Card
6-8 Weekly Treatment
Remsima™

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get.

Managing the Safety of Infliximab

Remsima™
Infliximab

HEALTHCARE
CELLTRION
A Ray of Excellence

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Infliximab may be associated with serious potentially life-threatening adverse reactions that need to be either prevented or identified and treated as early as possible.

This brochure includes

- **Details on the risk of serious and potentially life-threatening adverse reactions including tuberculosis (TB) and other serious infections**
- **Details of the Patient Alert Card**
- **Details of the patient Infusion Scheduler**

A patient screening sheet to provide guidance on appropriate screening and selection of patients is distributed together with this brochure.

To help mitigate the risk of TB in patients, Celltrion Healthcare has included a Patient Alert Card with each Pack of Remsima™ . This should be read in conjunction with the Package Information Leaflet. It is advisable to go through the Patient Alert Card with the patient or carer to ensure their understanding. (A copy of the Patient Alert Card can be found on the back page of this brochure).

It is important to record the batch number of the pack of Remsima administered to the patient.

In the event of an adverse drug reaction, include the batch number and brand name of the product administered in the report. An Infusion Scheduler is also available for patients to record the brand name and batch number of their infusion. (A copy of Infusion Scheduler can be found at the back of this brochure).

Refer to the SmPC for a full listing of adverse reactions.

These aides and further information can be requested from the local representative /
Local ADR reporting address:

Medical Logistics Ltd
No 8, Ivo Muscat Azzopardi Street, St. Julian's STJ 1905. Malta
Tel: 356 2755 9990
Email: safety@medicallogisticsltd.com

Risks Associated with Infliximab

- **Serious infections including sepsis and Opportunistic infections**

  Prevention:
  Infliximab is contra-indicated in patients with severe infections such as sepsis, abscesses, and opportunistic infections (e.g. pneumocystosis, candidiasis, listeriosis and aspergillosis) (see also below "Tuberculosis").
  Clinical experience shows that host defence against infection is compromised in some patients treated with infliximab. Patients taking tumour necrosis factor (TNF)-blockers, including infliximab are more susceptible to serious infections.
  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.

  Monitoring:
  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 must be monitored closely for infections 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.
  In patients treated with infliximab, invasive fungal infections such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if they develop a serious systemic illness. Invasive fungal infections may present as disseminated rather than localised disease, and antigen and antibody testing may be negative in some patients with active infection.

  Measures:
  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. If fungal infection is suspected 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.

- **Tuberculosis**

  Prevention:
  Infliximab is contra-indicated in patients with tuberculosis or other severe infections (see also "Serious infections including sepsis and Opportunistic infections")
  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 or interferon gamma release assay (IGRA), 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's alert card and the patient screening sheet.
  If active tuberculosis is diagnosed, infliximab therapy must not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of infliximab. In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, anti-tuberculosis therapy should be considered before the initiation of infliximab. Use of anti-tuberculosis 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.

  Monitoring:
  Patients must be monitored closely for tuberculosis during and after treatment with infliximab. Because the elimination of infliximab may take up to six months, monitoring should be continued throughout this period.

  Measures:
  All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g. night sweats, persistent cough, wasting/weight loss, low-grade fever) appear during or after infliximab treatment. Appropriate treatment should be undertaken, including tuberculostatic agents, immune stimulants etc.

- **Serious infusion reaction**

  Prevention:
  Infliximab has been associated with acute infusion-related reactions, including anaphylactic shock, and delayed hypersensitivity reactions (see also "Serum sickness (delayed hypersensitivity reaction)"). Acute infusion reactions including anaphylactic reactions may develop during (within seconds) or within a few hours following infusion. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.
  Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and a reduction in the frequency of infusion reactions. The effect of concomitant immunomodulator therapy was more profound in episodically-treated patients than in patients given maintenance therapy. Patients who discontinue immunosuppressants prior to or during infliximab treatment are at greater risk of developing these antibodies. Antibodies to infliximab cannot always be detected in serum samples.
  Limited experience from re-administration for psoriasis suggests a higher incidence of infusion reactions, including serious ones.

  Monitoring:
  Monitoring should be vigilant for the occurrence of anaphylactic and analphylactic -like symptoms. Symptoms of infusion reactions can consist of dyspnoea, urticaria, facial oedema, and hypotension.

  Measures:
  If acute infusion reactions occur, the infusion of infliximab must be interrupted immediately. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available.
  If an infusion reaction occurs in association with a shortened infusion, a slower infusion rate may be considered for future infusions if treatment is to be continued.

- **Serum sickness (delayed hypersensitivity reaction)**

  Prevention:
  Infliximab is contra-indicated in patients with a history of hypersensitivity to infliximab.
  Available data suggest an increased risk for delayed hypersensitivity with increasing infliximab free interval.

  Monitoring:
  Signs and symptoms of delayed hypersensitivity reactions can consist of myalgia and/or arthralgia with fever and/or rash, pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and headache. If patients are re-treated after a prolonged period (such as less than 1 year), they must be closely monitored for signs and symptoms of delayed hypersensitivity.

  Measures:
  Patients should be advised to seek immediate medical advice if they experience any delayed adverse event. Antibodies to infliximab cannot always be detected in serum samples. If serious reactions occur, symptomatic treatment must be given and further infliximab infusions must not be administered.

- **Lymphoma (excluding Hepatosplenic T-cell lymphoma)**

  Prevention:
  A risk for the development of lymphomas or other malignancies in patients treated with a TNF blocking agent cannot be excluded. Children and adults taking infliximab may have an increased risk of developing lymphoma or other cancer. Caution should be exercised when considering infliximab for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

  Monitoring and measures:
  The patients at increased risk for developing this condition should be closely monitored. In cases of such occurrence the therapy with infliximab should be considered for discontinuation. The condition should be treated in line with the contemporary oncological protocols.

- **Hepatosplenic T-Cell Lymphoma**

  Prevention:
  A risk for the development for hepatosplenic T-cell lymphoma in patients treated with infliximab cannot be excluded. The potential risk for the development for hepatosplenic T-cell lymphoma with the combination of Azathioprine (AZA) or 6-Mercaptopurine (6-MP) and infliximab should be carefully considered in patients with Crohn's disease or ulcerative colitis and above all in adolescent or young adult males.

  Monitoring and measures: Please, see 'Lymphoma' section for monitoring and measures.

- **Leukaemia**

  Prevention:
  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.

  Monitoring and measures: Please, see 'Lymphoma' section for monitoring and measures.

- **Paediatric malignancy**

  Prevention:
  A risk for the development of malignancies in children and adolescents treated with TNF blockers including infliximab cannot be excluded.
  Approximately half of the malignancies reported from children, adolescents and young adults were lymphomas. Rare post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF-blocking agents including infliximab. All infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were reported in adolescent or young adult males, treated also with AZA or 6-MP concomitantly with or immediately prior to infliximab . The potential risk with the combination of AZA or 6-MP and infliximab should be carefully considered.

  Monitoring and measures: Please, see 'Lymphoma' section for monitoring and measures.

Other serious risks

- **Congestive heart failure**

  Prevention:
  Infliximab is contra-indicated in patients with moderate or severe heart failure (New York Heart Association (NYHA) class III/IV). There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. 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.

  Monitoring:
  Infliximab should be used with caution in patients with mild heart failure (NYHA class I/II) and patients should be closely monitored.

  Measures:
  Infliximab must not be continued if new or worsening symptoms of heart failure occur. Heart failure should be treated according to the current medical standards, typically including cardiotonic agents, diuretics etc.

- **Demyelinating disorders**

  Prevention:
  In patients with pre-existing or recent onset of demyelinating or peripheral demyelinating disorders (including multiple sclerosis, optic neuritis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, or multifocal motor neuropathy) the benefits and risks of anti-TNF treatment should be carefully considered before initiation of infliximab therapy.

  Monitoring:
  Regular physical examination, including search for anamnestic data suggesting central nervous system (CNS) signs and symptoms should be carried out in patients treated with infliximab.

  Measures:
  Discontinuation of infliximab should be considered if these disorders develop. Appropriate symptomatic treatment for the neurological signs and symptoms should be considered.

- **Haematological reactions**

  Prevention:
  There have been reports of pancytopenia, leucopenia, neutropenia, and thrombocytopenia in patients receiving TNF-blockers, including infliximab.

  Monitoring:
  In all patients treated with infliximab, regular blood testing, at least blood cell count, should be performed. Common adverse reactions such as neutropenia, leucopenia and anaemia should be taken into consideration. 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) during treatment with infliximab.

  Measures:
  Discontinuation of infliximab therapy should be considered in patients with confirmed significant haematologic abnormalities. Appropriate therapy such as blood transfusion etc. should be considered.