Hepatitis B virus (HBV) reactivation

- Treatment with anti-TNFs, including infliximab may cause HBV reactivation in patients who carry this virus. In some cases, this can be life-threatening.
- Patients should be tested for HBV before starting treatment.
- HBV carriers should be closely monitored for signs and symptoms of reactivation during therapy, and for several months afterwards.
- Signs and symptoms of HBV reactivation include a sequential increase in HBV replication and the appearance of hepatic injury.
- Infliximab should be discontinued if HBV reactivation develops. Anti-viral therapy with appropriate supportive treatment should be initiated.

Hepatobiliary events

- In the post-marketing setting, there have been cases of jaundice and non-infectious hepatitis (some with features of autoimmune hepatitis) with infliximab. This should be taken into consideration when starting infliximab treatment.
- Patients receiving infliximab who show signs and symptoms of liver dysfunction should be evaluated for evidence of liver injury.
- In general, patients who developed alanine transaminase (ALT) and aspartate transaminase (AST) elevation were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of infliximab or modification of concomitant therapy.
- Infliximab should be discontinued if jaundice and/or ALT elevations ≥5 times the upper limit of normal develop, and a thorough investigation of the abnormality should be undertaken.

Intestinal and perianal abscess (Crohn's disease)

- Patients who have fistulising Crohn's disease with acute supportive fistulas must not start treatment with infliximab until sources of possible infection (specifically abscess) have been excluded.
- Patients should have a regular physical examination, including a search for anamnestic data suggesting the occurrence of fistulae.
- Discontinuation of infliximab should be considered if this condition develops. Appropriate surgical procedures should be carried out.

Systemic lupus erythematosus/lupus-like syndrome

- The relative deficiency of TNFα caused by anti-TNF therapy may result in the initiation of an autoimmune process.
- Symptoms include fatigue, joint pain, or a rash on the cheeks or arms that is sensitive to the sun.
- Infliximab should be discontinued if a patient develops symptoms suggestive of a lupus-like syndrome, and is positive for antibodies against double-stranded DNA. Symptomatic treatment (e.g. anti-inflammatory agents, local corticosteroids) should be given.

Vaccinations

- There are limited data on the response to live vaccines in patients treated with infliximab. Live vaccines should therefore not be given with infliximab.
- 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.

Pediatric patients

In children and adolescents aged 6 to 17 years, Remsima is indicated for:

- severe, active Crohn's disease in patients who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies.
- severely active ulcerative colitis in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contra-indications for such therapies.

Pediatric malignancy

- The risk of developing cancer cannot be excluded in children and adolescents treated with
- anti-TNFs, including infliximab. Approximately half the cancers reported in children, adolescents and young adults were lymphomas.
- Cases of HSTCL have been reported with anti-TNFs, including infliximab. The vast majority of
- cases in patients receiving infliximab were in patients with Crohn's disease or ulcerative colitis; most of these were in adolescent or young adult males who received AZA or 6-MP concomitantly with, or immediately before, infliximab.
- Patients who are at increased risk should be closely monitored. If cancer develops, discontinuation of infliximab should be considered.

Infection

- In clinical studies, infections have been reported in a higher proportion of pediatric patients than adult patients.

Vaccinations

- There are limited data on the response to live vaccines in patients treated with infliximab. Live vaccines should therefore not be given with infliximab.
- There is an increased risk of infection in pediatric patients. It is therefore important that they are up-to-date with their vaccinations before starting infliximab.
- 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.

Reference
Remsima® (Infliximab), Summary of Product Characteristics.
Version 1.0- 07/2018

Important Safety Information for Infliximab

Remsima®
Infliximab

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 potentially life-threatening adverse reactions including tuberculosis (TB) and other serious infections

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.

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.

The information in this brochure does not replace the full prescribing information in the Summary of Product Characteristics, which should be read and understood before prescribing infliximab.

Reporting of side effects

Patient safety is a top priority for JPI. JPI is committed to continuously monitor the safety and tolerability of its therapies, and to keep close communication with health authorities and healthcare professionals in order to provide them with accurate information about any potential risks associated with the use of its products. You can assist for monitoring the safety of Remsima® (Infliximab) by reporting suspected adverse events associated with the use of Remsima® to:

Saudi Food and Drug Authority National Pharmacovigilance and Drug Safety Center Fax: +966-11-205-7662. Toll-free Phone: 19999 Email: npc.drug@sfda.gov.sa

Website: https://ade.sfda.gov.sa/Or; Qualified Person for Pharmacovigilance Sahar Abdulmajeed Al-Hamad. Jazeera Pharmaceutical Industries (JPI). E-mail: salhamad@hotmail.com Tel: +966(11) 4173731 Ext: 1086. Mobile: +966506515948.

Tuberculosis

- Infliximab is contraindicated in patients with TB.
- Before starting treatment, patients must be screened for active and latent TB. Screening should include appropriate tests (e.g. tuberculin skin test, chest X-ray or interferon gamma release assay) and a detailed medical history.
- If screening reveals active TB, infliximab therapy must not be started.
- If screening reveals latent TB, anti-TB therapy must be started before initiation of infliximab. Anti-TB therapy should also be considered in patients with a history of active or latent TB, but in whom adequate treatment cannot be confirmed.
- Patients should be monitored for TB during and after treatment with infliximab. Elimination of infliximab can take up to six months, so monitoring should continue during this time.
- Patients should be advised to seek medical advice if they develop symptoms suggestive of TB (e.g. night sweats, persistent cough, wasting/weight loss, low-grade fever) during or after treatment. If such symptoms develop, patients should be given appropriate treatment (tuberculostatic agents, immune stimulants, etc.).

Other serious infections (including sepsis and opportunistic infections)

- Infliximab is contraindicated in patients with severe infections (e.g. sepsis, abscesses) or opportunistic infections (e.g. pneumocystosis, candidiasis, listeriosis and aspergillosis).
- Patients taking an anti-TNF (including infliximab) are more susceptible to serious infection.
- Caution should be exercised when considering infliximab therapy in patients with a chronic infection or a history of recurrent infections. Patients should be advised of, and avoid exposure to, potential risk factors for infection (as appropriate).
- Patients should be monitored for infection during and after treatment with infliximab. Elimination of infliximab can take up to six months, so monitoring should continue during this time.
- If patients develop a serious systemic illness, an invasive fungal infection (e.g. aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis) should be suspected. These infections may present as disseminated rather than localised, and antigen and antibody testing may be negative in patients with active infection.
- Infliximab should be discontinued if a patient develops a new serious infection or sepsis. Appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

Serious infusion reaction

- Infliximab has been associated with acute infusion-related reactions (including anaphylactic shock) and delayed hypersensitivity reactions (see below). Acute infusion reactions may develop during the infusion, or within a few hours afterwards. Patients may be pre-treated with anti-histamines, hydrocortisone, and/or paracetamol to prevent mild and transient eff
- Antibodies to infliximab have been associated with an increased frequency of infusion reactions. Concomitant administration of immunomodulators is associated with a lower incidence of antibodies and a reduced frequency of infusion reactions. This effect is more profound in episodically-treated patients than in patients receiving maintenance therapy.
- Limited data in psoriasis patients show that the risk of infusion reactions (including serious ones) is greater following re-administration compared with maintenance therapy.
- Patients should be monitored for signs of anaphylactic and anaphylactic-like symptoms. Symptoms of infusion reaction include dyspnea, urticaria, facial edema and hypotension.
- The infliximab infusion should be stopped immediately if an acute infusion reaction occurs. Emergency equipment (adrenaline, corticosteroids, antihistamines, artificial airway) must be available.
- If an infusion reaction occurs during a shortened infusion, a slower infusion rate may be considered for future infusions (if treatment is to continue).

Serum sickness (delayed hypersensitivity reaction)

- Infliximab is contraindicated in patients with a history of hypersensitivity to infliximab.
- Available data suggest an increased risk for delayed hypersensitivity with increasing infliximab-free interval. If patients are re-treated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.
- Signs and symptoms of delayed hypersensitivity include: myalgia and/or arthralgia with fever and/or rash; pruritus; facial, hand, or lip edema; dysphagia; urticaria; sore throat; headache.
- Patients should be advised to seek immediate medical advice if they experience any delayed adverse event.
- If a serious reaction occurs, patients should be given symptomatic treatment. Further infliximab infusions should not be administered.

Malignancies (excluding hepatosplenic T-cell lymphoma)

- The risk of developing lymphoma, melanoma, Merkel cell carcinoma or other cancers cannot be excluded in patients treated with anti-TNFs. In the post-marketing setting, cases of leukemia have been reported in patients treated with an anti-TNF. Patients taking infliximab may have an increased risk of developing lymphoma, melanoma, Merkel cell carcinoma or other cancers. Patients with long-standing, highly active inflammatory rheumatoid arthritis have an increased background risk for leukemia and lymphoma.
- Caution should be exercised when considering infliximab for patients with a history of cancer, and when considering continued treatment in patients who develop cancer.
- Patients who are at increased risk should be closely monitored. If cancer develops, discontinuation of infliximab should be considered.

Hepatosplenic T-cell lymphoma (HSTCL)

- The risk of developing HSTCL cannot be excluded in patients treated with anti-TNFs.
- The potential risk associated 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 (particularly adolescent or young adult males).
- Patients who are at increased risk should be closely monitored. If HSTCL develops, discontinuation of infliximab should be considered.

Congestive heart failure

- Infliximab is contraindicated 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 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.
- Infliximab should be used with caution in patients with mild heart failure (NYHA class I/II) and patients should be closely monitored.
- Infliximab must be discontinued if new or worsening symptoms of heart failure occur. Patients should receive treatment according to current medical standards.

Demyelinating disorders

- Anti-TNF treatment has been associated with cases of new onset, exacerbations of, and/or
- radiographic evidence of central nervous system demyelinating disorders (including multiple sclerosis), and peripheral demyelinating disorders (including Guillain-Barré syndrome).
- The benefits and risks of anti-TNF treatment should be carefully considered before starting therapy in patients with pre-existing or recent onset demyelinating disorders.
- Patients should have regular physical examinations, including a search for anamnestic data suggesting central nervous system signs and symptoms.
- Discontinuation of infliximab should be considered if demyelinating disorders develop. Appropriate symptomatic treatment should be considered.

Hematological reactions

- Pancytopenia, leucopenia, neutropenia and thrombocytopenia have been reported in patients receiving anti-TNFs, including infliximab.
- Patients should have regular blood tests.
- Patients should be advised to seek immediate medical advice if they experience any signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor).
- Discontinuation of infliximab should be considered in patients with confirmed significant hematologic abnormalities. Appropriate therapy, such as blood transfusion, should be considered.

Sarcoidosis/sarcoid-like reaction

- Infliximab should be discontinued if a patient develops symptoms suggestive of a sarcoid-like reaction (although this has been observed rarely in patients treated with infliximab. Appropriate symptomatic treatment (e.g. bronchodilators, mucolytic agents, antibiotics, etc.) should be given.
- Patients should be monitored for signs and symptoms suggesting the development of sarcoidosis or a sarcoid-like reaction (usually dyspnea or cough; sometimes skin rashes).